QNEXA®
(Phentermine / Topiramate)
Extended Release Capsules

Endocrinologic and Metabolic Drugs

Advisory Committee Meeting

February 22, 2012

VIVUS, Inc.

QNEXA in Context of Other Obesity Pharmacotherapies

- 10% weight loss
- Reduction in blood pressure

Sponsor Presentation Outline

Introduction	**Peter Tam, MBA** President, VIVUS
Efficacy	**Wesley W. Day, PhD** Vice President, Clinical Development, VIVUS; Adjunct Associate Professor, University of Maryland at Baltimore
Safety	**Neil Gesundheit, MD, MPH** Clinical Advisor; Former CMO, VP Clinical & Regulatory Affairs; Associate Professor, Stanford University School of Medicine
CRL: **Heart Rate/MACE**	**Peter Kowey, MD** Professor of Medicine & Clinical Pharmacology, Jefferson Medical College of Thomas Jefferson University
CRL: **Teratogenicity of Topiramate**	**Gary Shaw, PhD** Professor of Pediatrics Neonatal and Developmental Medicine, Stanford University School of Medicine
Teratologist's Perspective	**Anthony Scialli, MD** Clinical Professor of Obstetrics and Gynecology, George Washington Univ. School of Medicine; Director, Reproductive Toxicology Center, DC
Cardiologist's Perspective	**A. Michael Lincoff, MD** Vice Chairman, Dept of Cardiovascular Medicine, The Cleveland Clinic Professor of Medicine, Case Western Reserve University
Medical Perspective, **Risk / Benefit**	**Arya Sharma, MD, PhD** Professor of Medicine Chair for Obesity Research & Management University of Alberta, Royal Alexandra Hospital

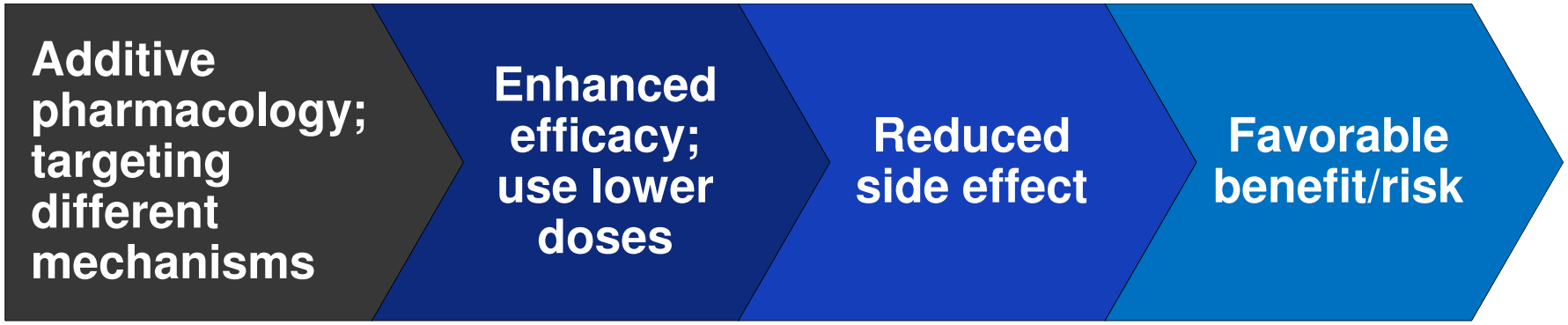
Sponsor Presentation Outline (Cont'd)

REMS	FDA
Risk Management	Barbara Troupin, MD Sr. Director, Global Medical Affairs, VIVUS

Phentermine and Topiramate Experience

- **Phentermine**
  - Short-term weight loss (1959)
  - Two recent FDA approvals (2011)
- **Topiramate**
  - Epilepsy (1996), migraine prophylaxis (2004)
  - Pediatric epilepsy monotherapy (2011)

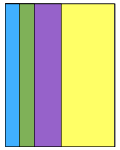
Rationale for Combination of Phen/TPM Diverse Pharmacology, Complementary Effects



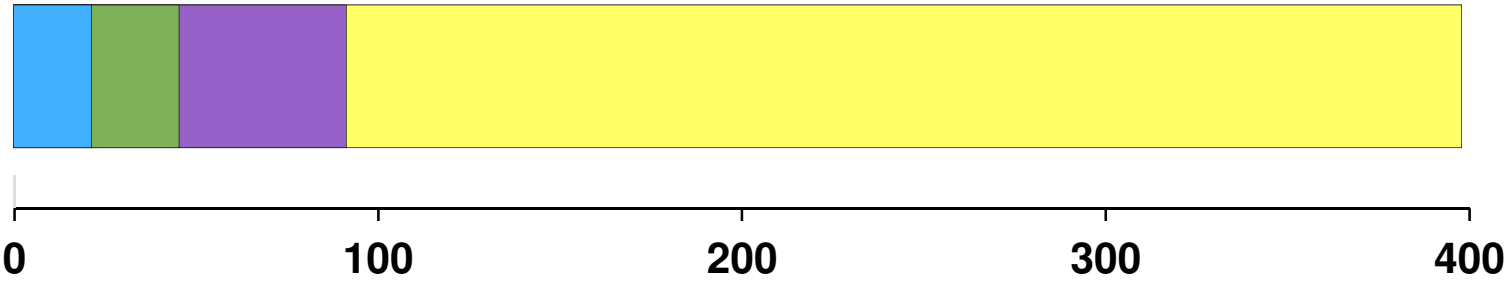
Results of clinical trials with QNEXA confirmed hypothesis

QNEXA (Phentermine / Topiramate ER): A Novel Combination Treatment Containing Lower Doses of Two Approved Agents

Phentermine (Maximum approved dose, 30 mg)



Topiramate (Maximum approved dose, 400 mg)



QNEXA Low (3.75/23)	Starting dose
QNEXA Mid (7.5/46)	Recommended dose
QNEXA Top (15/92)	For patients not achieving weight-loss goal

Regulatory History: Topics Reviewed with EMDAC in 2010

- Psychiatric effects
- Cognitive effects
- Bicarbonate decreases
- Heart rate increases
- Teratogenic risk

Regulatory History: Topics Reviewed with EMDAC in 2010

- Psychiatric effects
- Cognitive effects
- Bicarbonate decreases
- **Heart rate increases**
- **Teratogenic risk**

Regulatory History: Complete Response Letter (CRL)

- **Heart rate**
  - Provide evidence elevations in heart rate on QNEXA (0.6 to 1.6 bpm) do not increase risk for MACE
  - Provide 2-year data
- **Teratogenicity**
  - Assess teratogenic potential of topiramate and QNEXA
  - Provide detailed REMS for teratogenicity

Regulatory History: NDA Resubmission with Contraindication

- **VIVUS NDA resubmission (Oct 2011)**
  - **Contraindication in WOCBP**
- **FDA recommendations (Dec 2011)**
  - **Remove contraindication in WOCBP because the benefits of QNEXA in some women may outweigh the risks**
  - **Develop a rigorous REMS focusing on education**

Proposed Indication

- **Treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise**
- **Recommended for**
  - **Obese patients (BMI ≥30 kg/m^2)**
  - **Overweight patients (BMI ≥27 kg/m^2) with weight-related co-morbidities, such as**
    - **Hypertension**
    - **Type 2 diabetes**
    - **Dyslipidemia**
    - **Central adiposity**

Proposed Contraindication, Pregnancy Category and Warnings

- **Contraindication**
  - Women who are pregnant
    - If you become pregnant while on QNEXA, treatment must be stopped immediately
- **Category X**
  - Re-classification of all weight loss medications
  - Consistent with clinical guidelines for weight gain and recommendations against weight loss during pregnancy
- **Warnings**
  - Women at risk of becoming pregnant not using effective contraception

QNEXA Development
Weight Loss and
Weight-Related Co-Morbidities

Wesley W. Day, PhD
Vice President, Clinical Development
VIVUS, Inc.

Adjunct Associate Professor
University of Maryland at Baltimore
School of Pharmacy

Efficacy Presentation Outline

- Pivotal studies OB-302 and OB-303 (1 year)
  - Design, disposition and weight loss
- OB-305 (2 years)
  - Design, disposition and weight loss
- Weight-related co-morbidities
  - Co-morbidity changes in all patients
  - Patients with hypertension or diabetes
  - Reduction in cases of new-onset diabetes
- Effects on QOL
  - IWQOL & SF-36

QNEXA Phase 3 Program

Factorial and Pivotal Studies for Weight Loss

Phase 3 Program

Pivotal Studies

	OB-301	OB-302	OB-303	OB-305
Overview	Factorial combination	Severely obese	Weight & comorbidities	2-year safety and efficacy
N	756	1267	2487	675
BMI	30 - 45	≥35	27 – 45 with comorbidities	27 – 45 with comorbidities
Length	6 months	1 year	1 year	2 years
Lifestyle Modification Program	Learn® Program plus 500 kcal/day reduction			

Pivotal Studies: Baseline Demographics

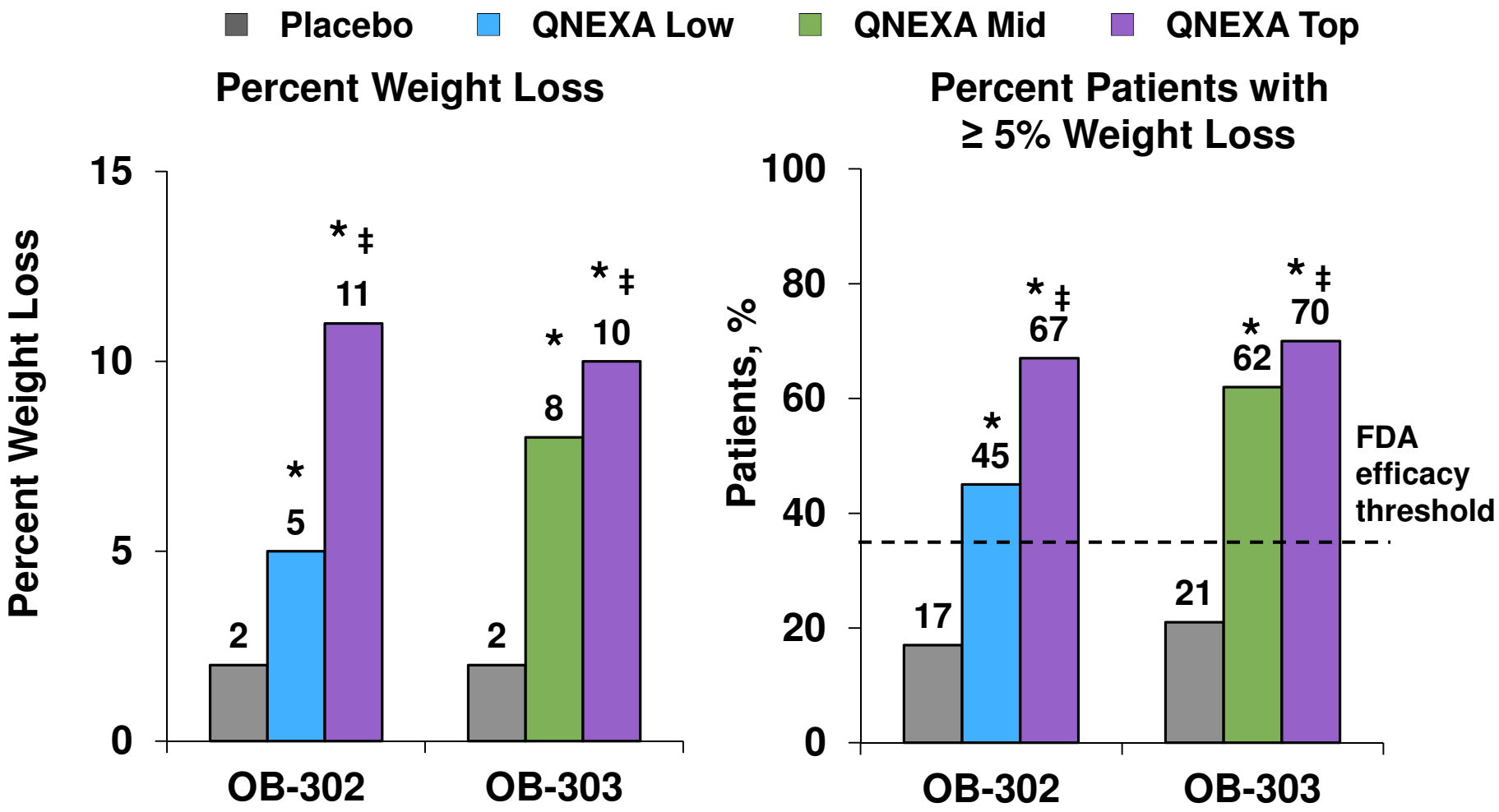
Demographics	OB-302	OB-303
BMI, kg/m^2 (mean ± SD)	42 ± 6	37 ± 5
Age, years (mean ± SD)	43 ± 12	51 ± 10
Female gender, %	83	70
Race, %		
Caucasian	80	86
African American	18	12
Asian / Other	3	3
Ethnicity, % Hispanic	15	13
History of, %		
Hypertension	25	69
Dyslipidemia	19	57
Diabetes	0	16

Treatment arms balanced for their respective studies

Pivotal Studies: Patient Disposition

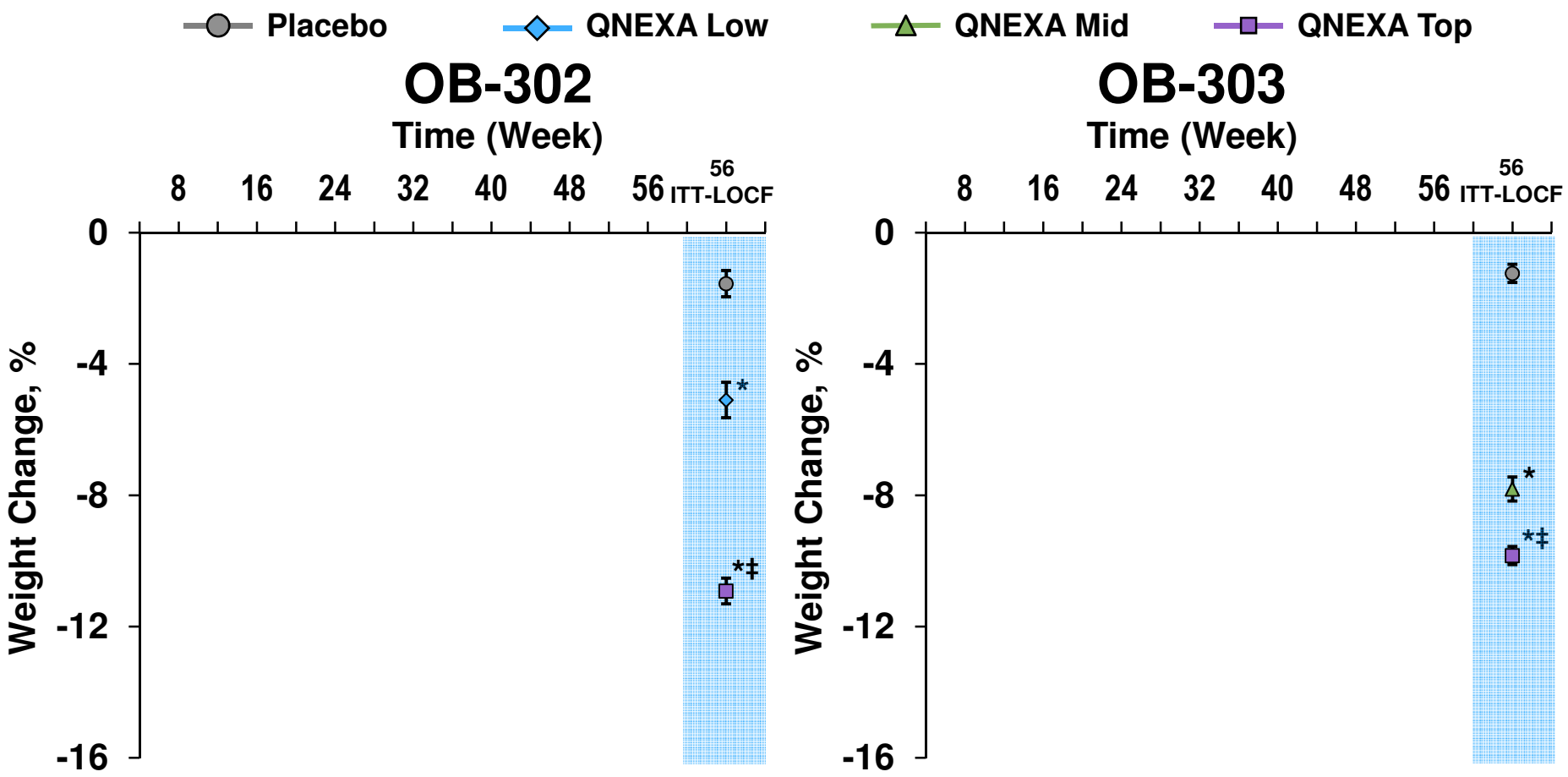
Percent	Placebo N=1,508	QNEXA Dose Low N=241	Mid N=498	Top N=1,507
ITT	98	97	98	98
Completed Study	59	61	75	71
Completed Study on Drug	53	57	69	62

Pivotal Studies: Co-Primary Endpoints ITT LOCF at Week 56



*p<0.0001 vs placebo; ‡p<0.002 vs low/mid dose

Pivotal Studies: Weight Loss Over Time (All Observed Data)



All observed data; *p<0.0001 vs placebo; ‡p<0.0001 vs QNEXA Mid or Low

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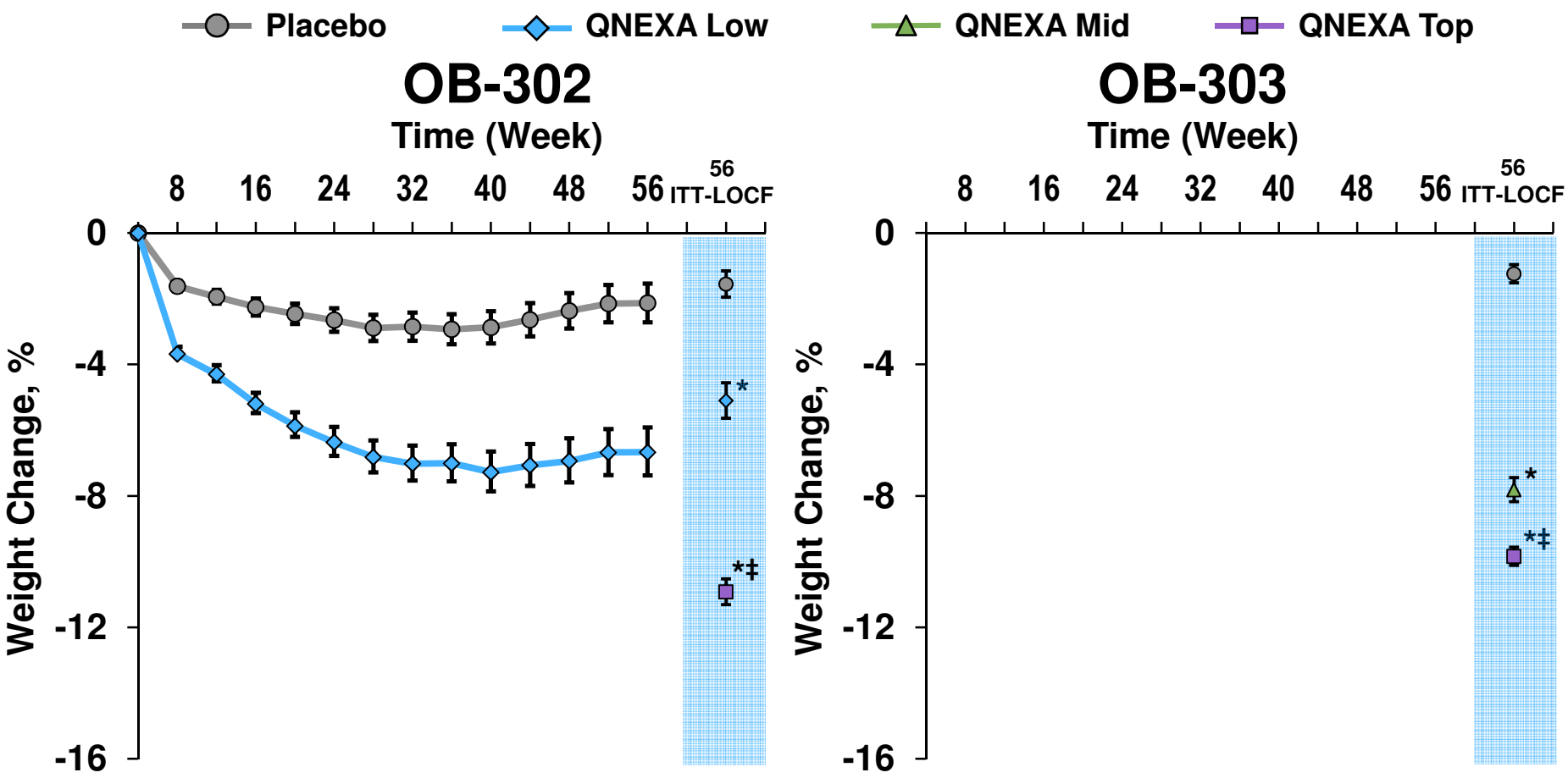

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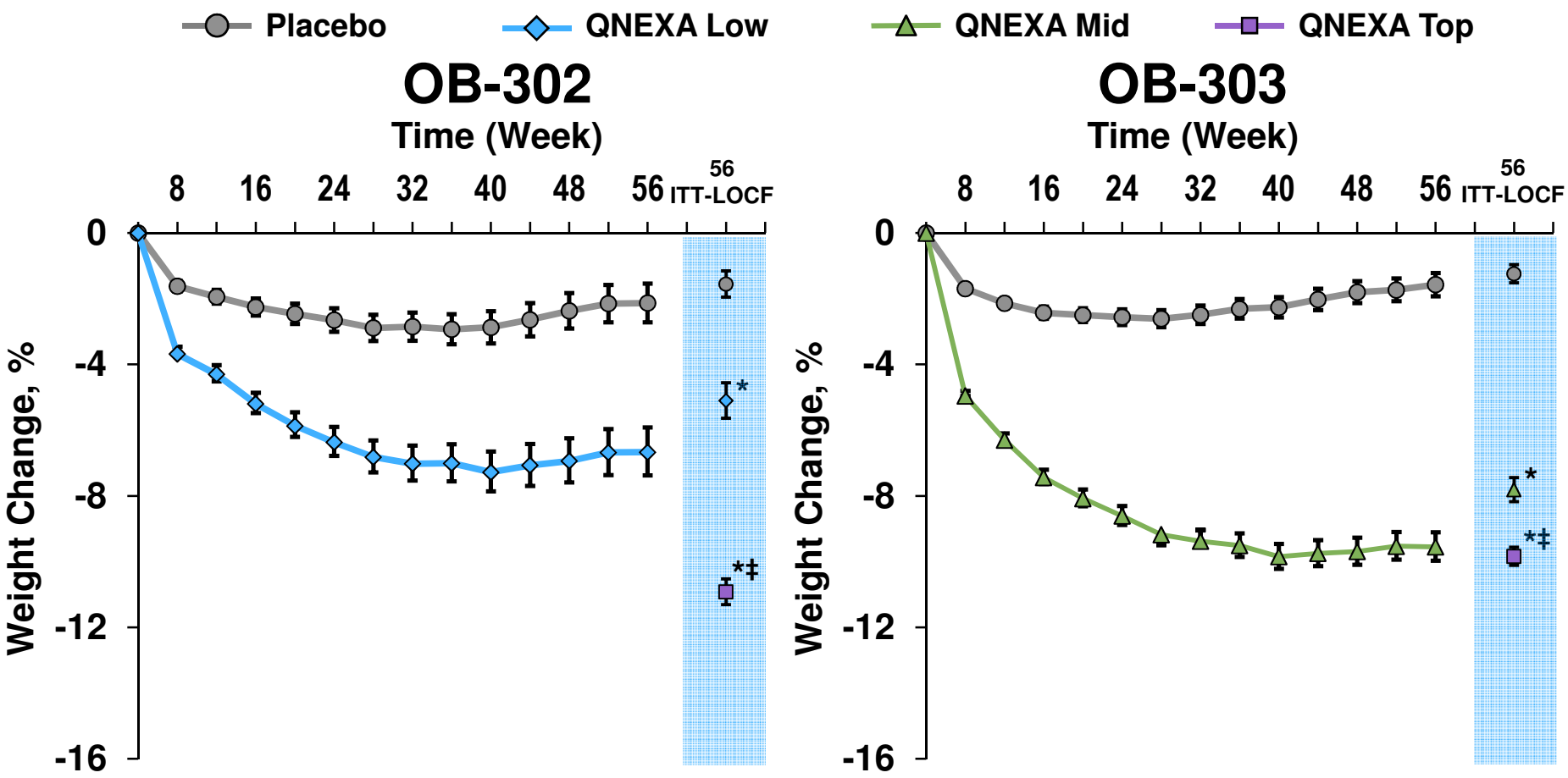

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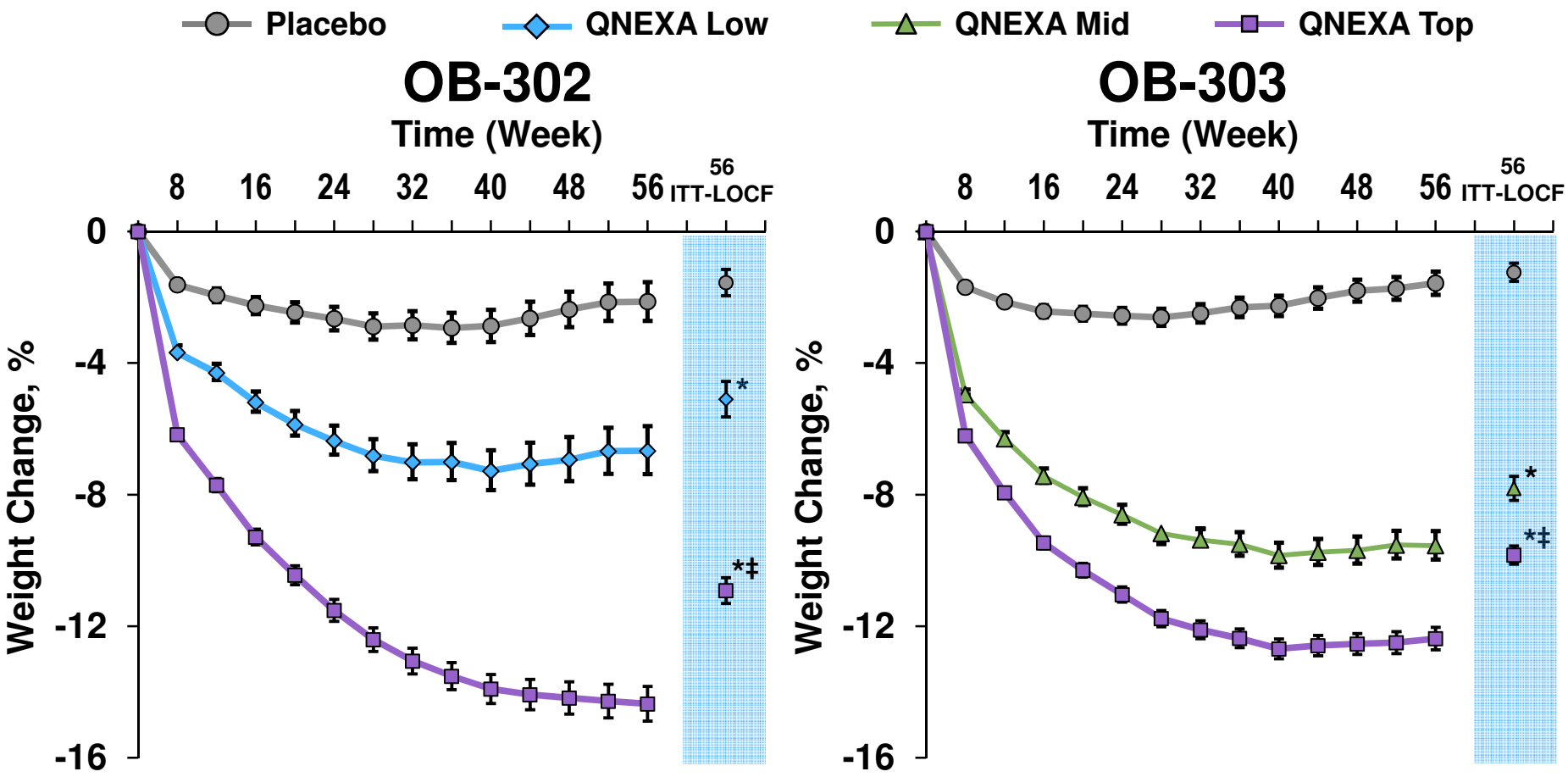


All observed data; *p<0.0001 vs placebo; ‡p<0.0001 vs QNEXA Mid or Low

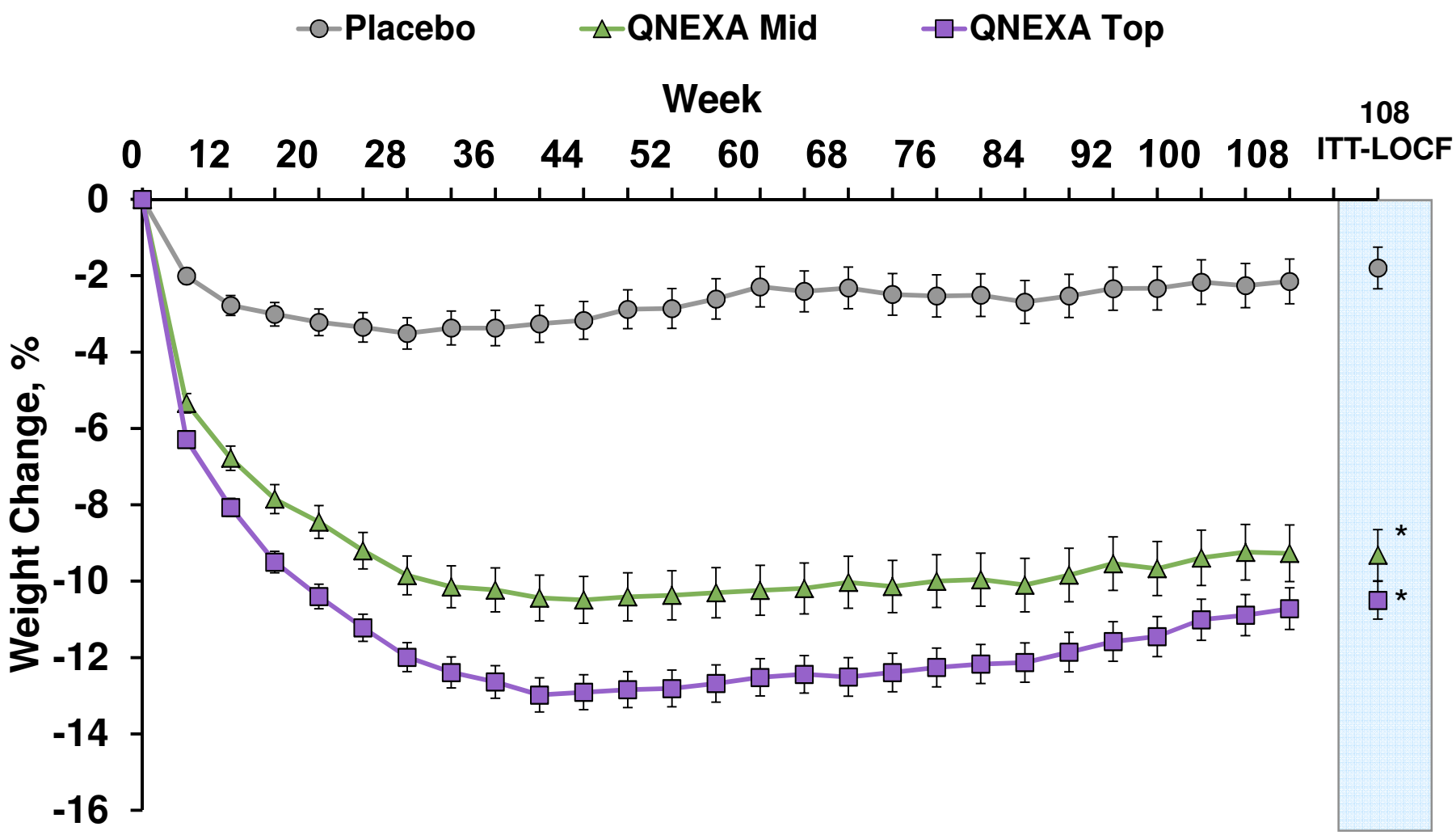
OB-305:
2-Year Weight Loss Study

OB-305: 2-Year Study

- **Continuation of OB-303 at high-enrolling centers**
  - 36 of 92 OB-303 sites participated
  - 676 of 866 eligible patients (78%) elected to enroll

		QNEXA	
	Placebo	Mid	Top
Eligible for OB-305 (n)	327	194	345
Enrolled, n (%)	227 (69)	154 (79)	295 (86)
Completed, n (%)	197(87)	129 (84)	248 (84)

2-Year Cohort (All Observed Data) Percent Weight Change Over time



Completers & ITT-LOCF , *p<0.0001 vs placebo

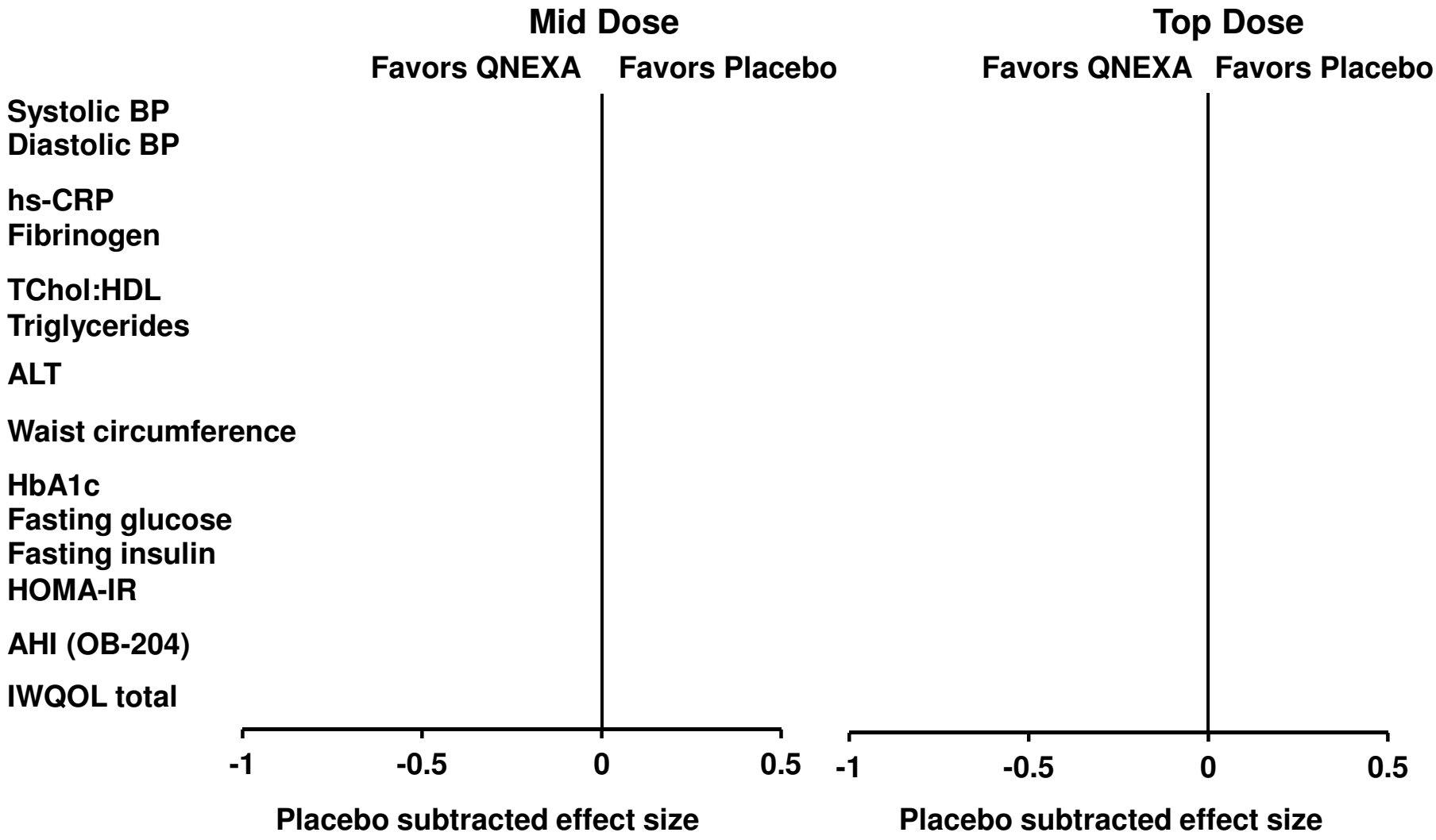
Effects on Weight-Related Co-Morbidities

Hypertension

Diabetes

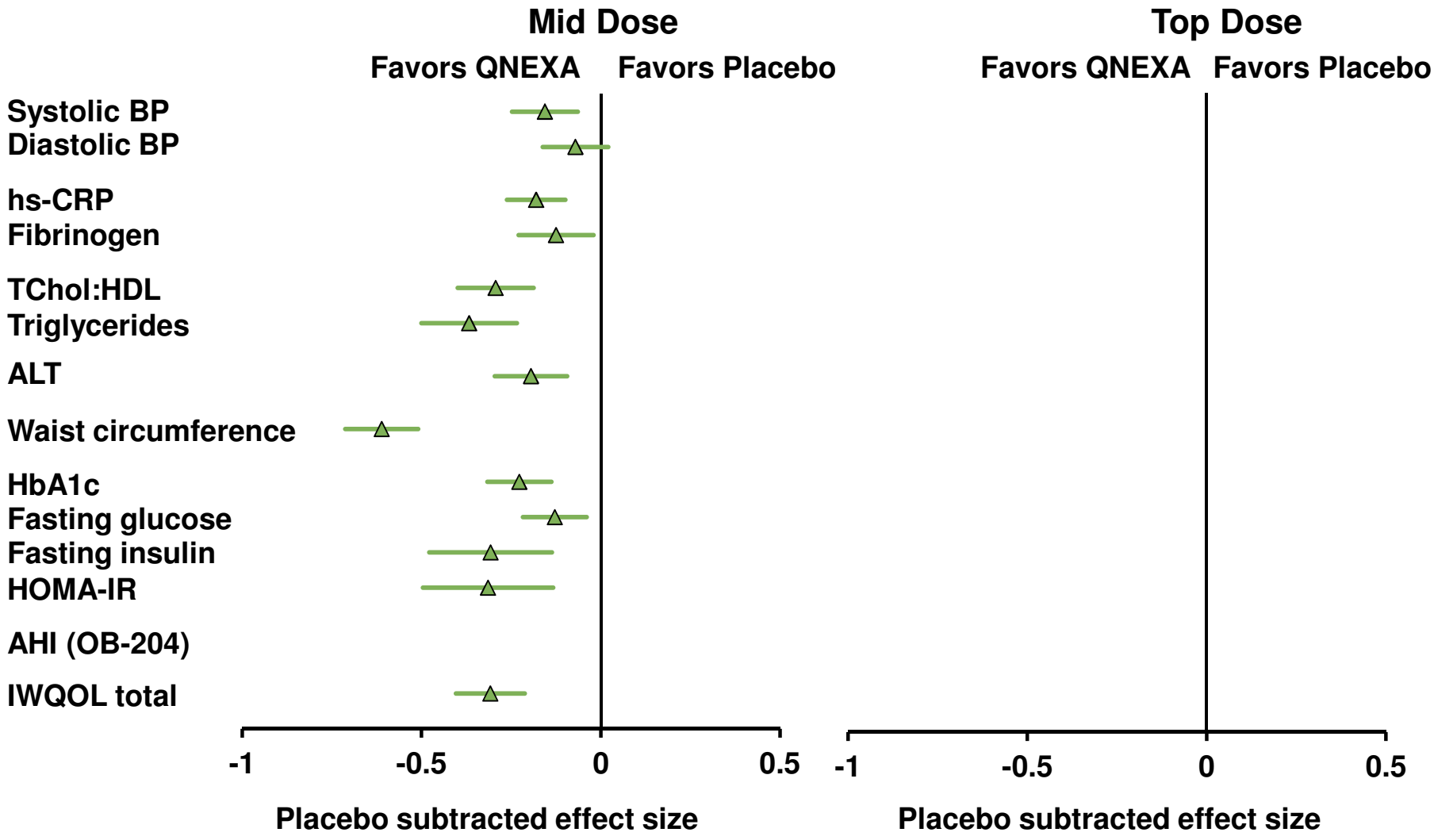
New-Onset Diabetes

Pivotal Studies: Effects on Weight-Related Co-Morbidities



ITT-LOCF; Effect size calculated as mean change divided by SD

Pivotal Studies: Effects on Weight-Related Co-Morbidities



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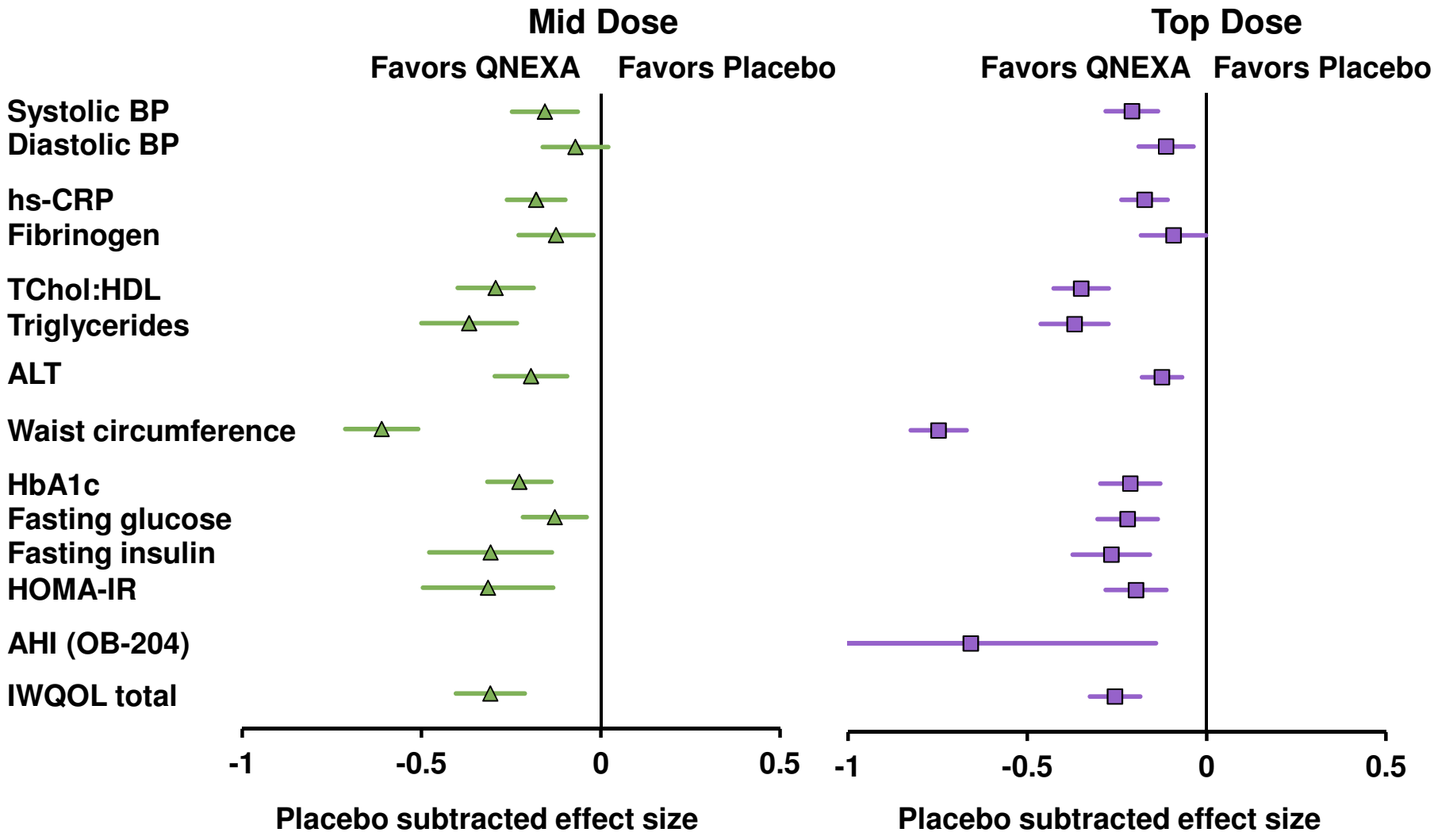

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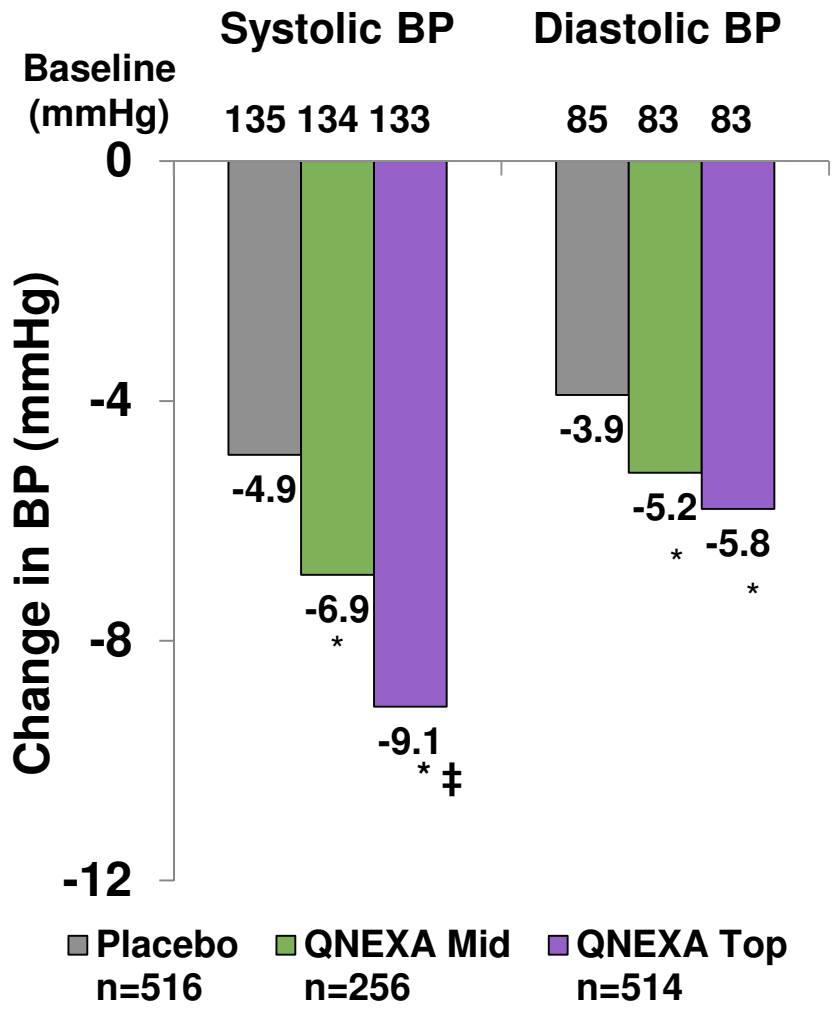
Patients with Hypertension: Changes in BP and Anti-Hypertensive Medications

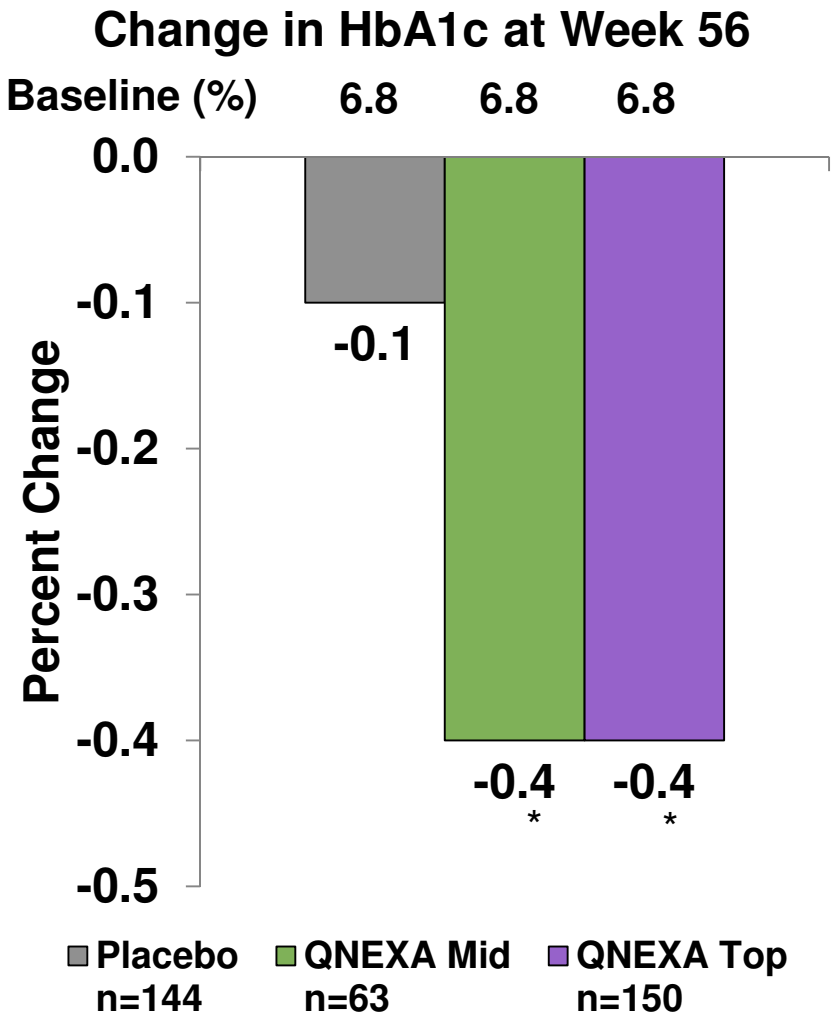


Anti-Hypertensive Medications

Patients, %	Placebo	QNEXA Mid	QNEXA Top
Starting new	8.1	3.9	4.3
Discontinuing existing	4.7	10.5	14.8

ITT-LOCF (OB-303); *p<0.05 vs placebo; ‡p<0.05 vs QNEXA Mid

Patients with Diabetes: Changes in HbA1c and Anti-Diabetic Medications

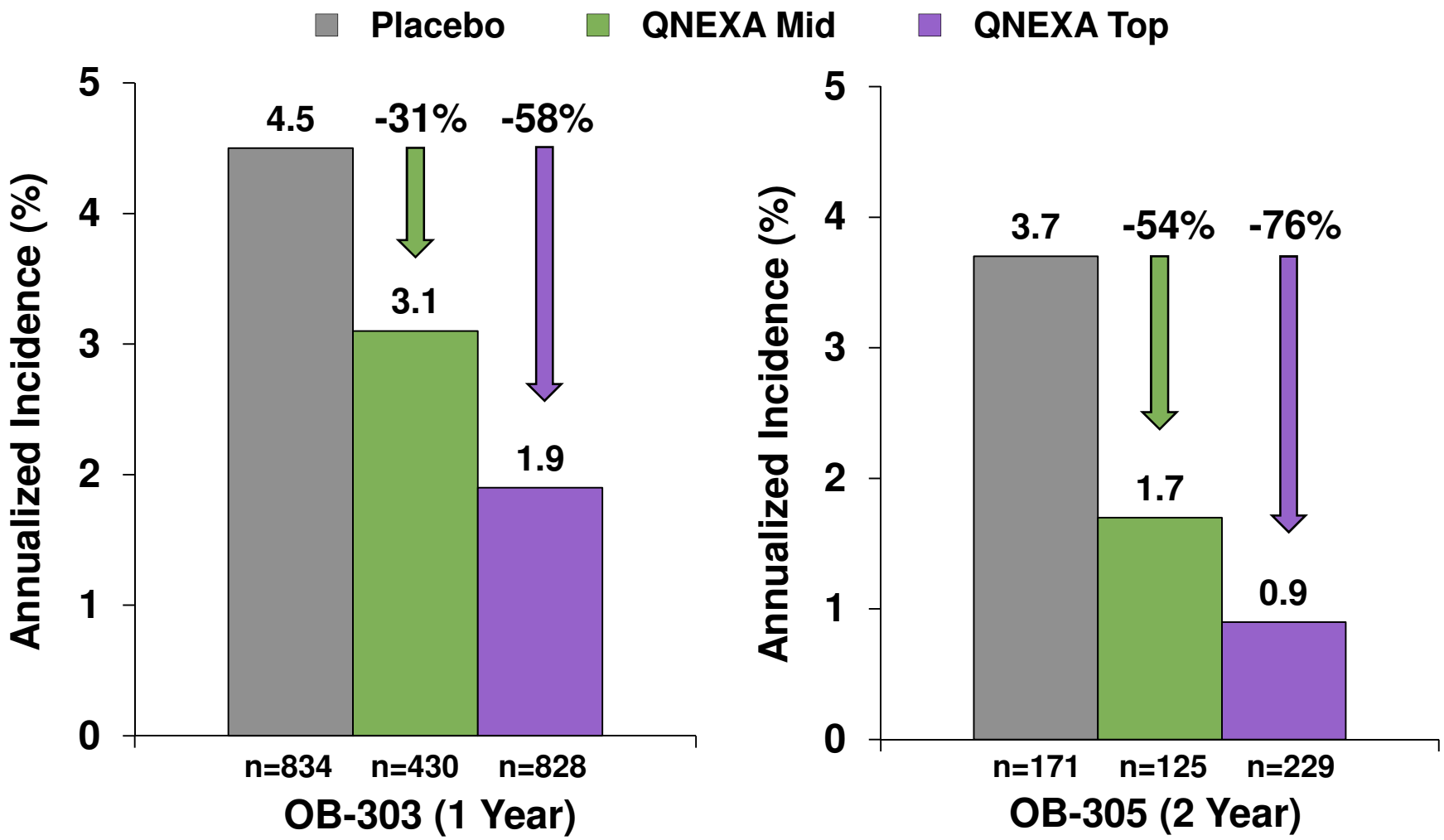


ITT-LOCF (OB-303); *p<0.05 vs placebo

Anti-Diabetic Medications

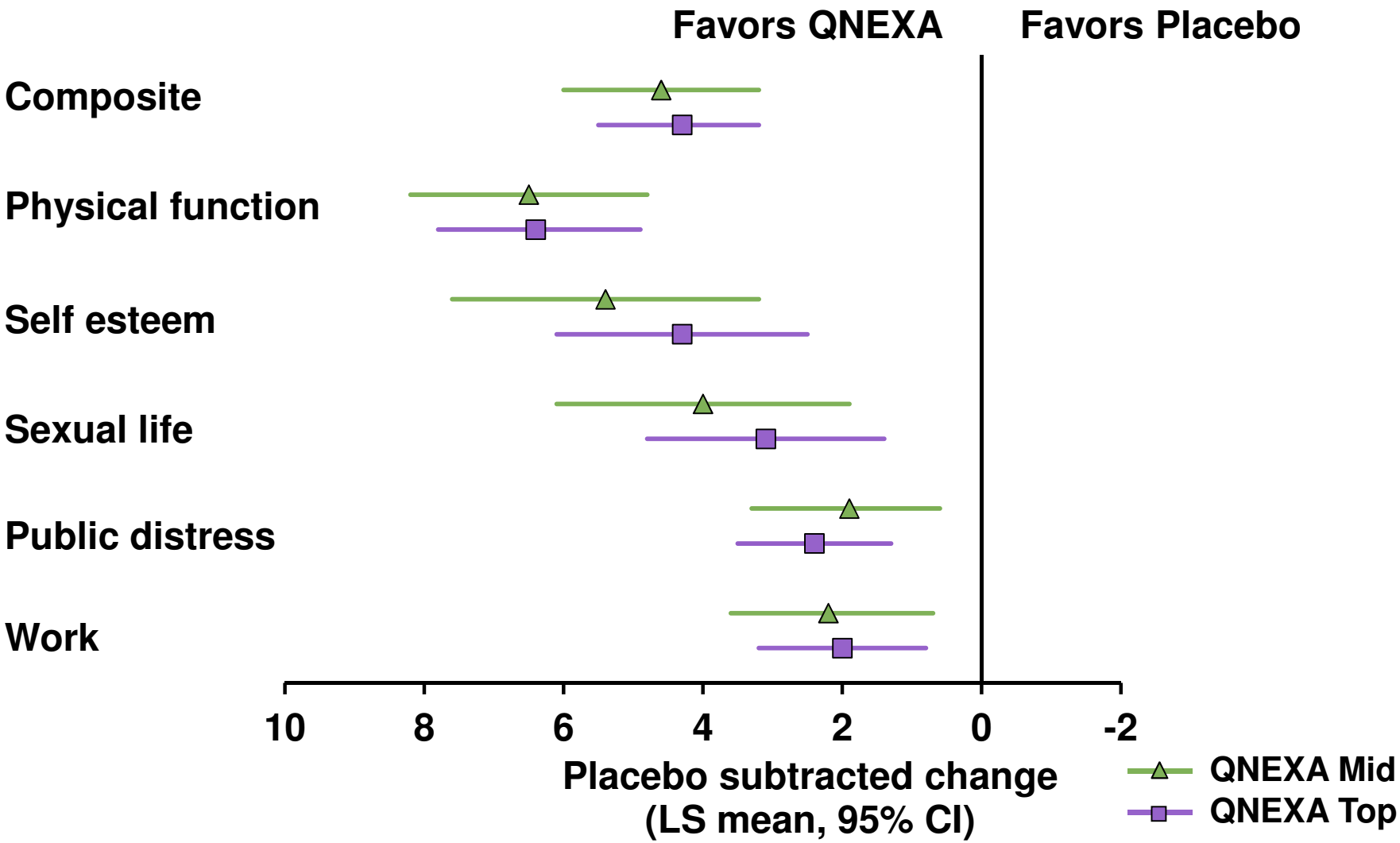
Patients, %	Placebo n=157	QNEXA Mid n=67	QNEXA Top n=164
Starting new	14.6	4.5	4.3
Discontinuing existing	2.5	3.0	3.7

Patients Without Diabetes: Progression to Diabetes

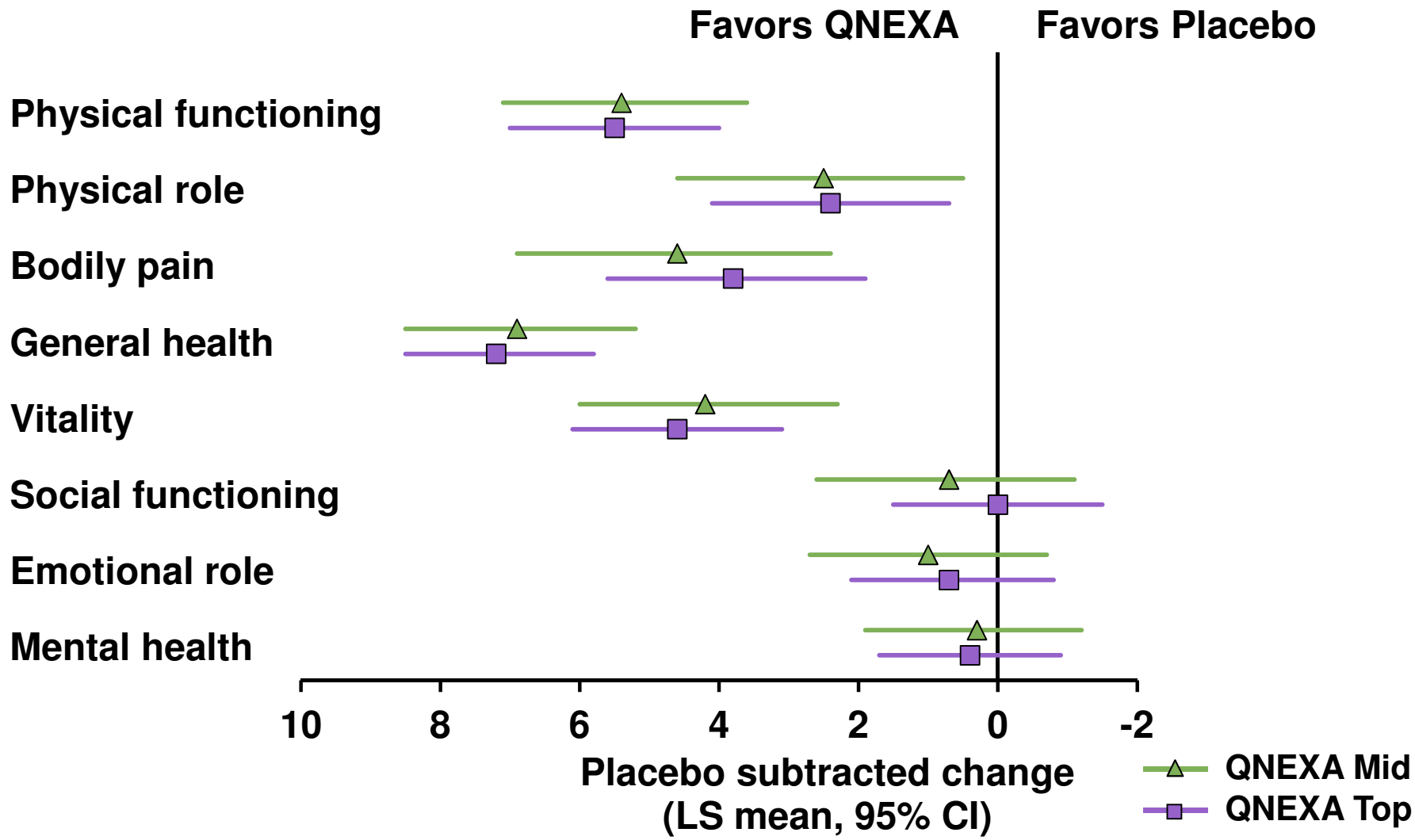


*Progression to diabetes defined as ≥2 consecutive visits with fasting glucose ≥126 mg/dL or 2-hour post oral glucose tolerance test glucose ≥200 mg/dL

OB-303:
Impact of Weight on QOL (IWQOL)



OB-303:
Quality of Life (SF-36 Domain Scores)



SF-36=Short Form (36) health survey

Efficacy Conclusions

- Weight-loss results (>10%) met and exceeded FDA and NIH efficacy bench marks
- Weight-loss was sustained over 2 years of treatment
- Weight-loss is associated with clinically meaningful improvements in QOL as well as CV and metabolic risk factors
- A reduction in progression to diabetes observed in pivotal and 2-year studies

General Safety

Neil Gesundheit, MD, MPH

Clinical Advisor to the Sponsor
Former VP & Chief Medical Officer
Clinical Research & Regulatory Affairs

Associate Professor of Medicine (Endocrinology)
Stanford University

Safety Presentation Outline

- Phentermine / Topiramate general safety
- 1-year cohort vs 2nd year (OB-305)
  - Common AEs
  - Disposition and AEs leading to discontinuation
  - SAEs
- Safety concerns from 7/15/10 EMDAC meeting
  - Psychiatric TMEs
  - Cognition TMEs
  - Lowering of serum bicarbonate
  - Increase in heart rate
  - Teratogenicity

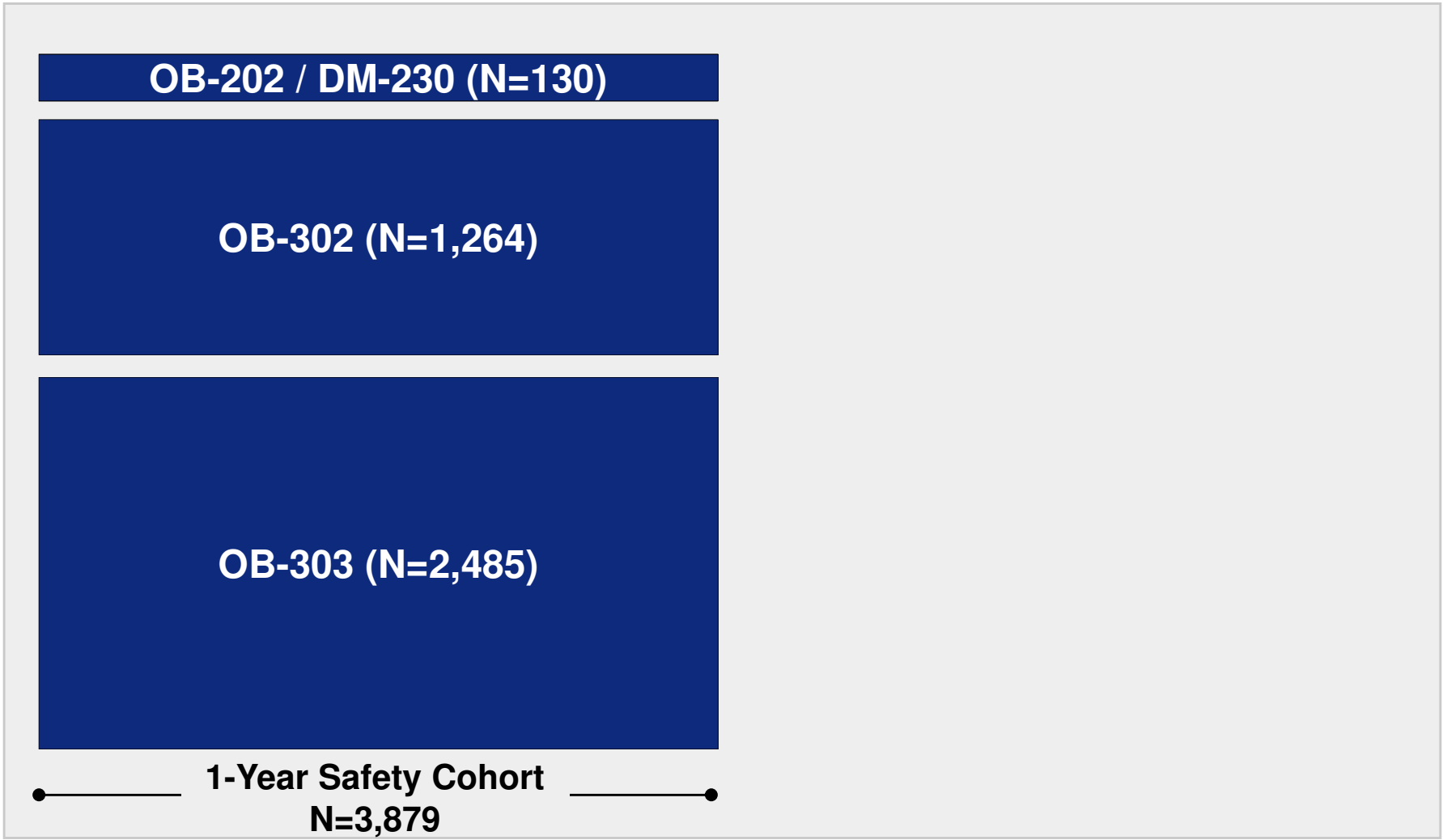
Known Side-Effects Associated with Phentermine and Topiramate

- **Phentermine[1]**
  - Dry mouth
  - Insomnia
  - Headache
  - Dizziness
  - Fatigue
  - Palpitation
- **Topiramate[2]**
  - Paresthesia
  - Fatigue
  - Nausea / Diarrhea
  - Dizziness
  - Dysgeusia
  - Somnolence
  - Attention / language / memory
  - Depression / anxiety / mood

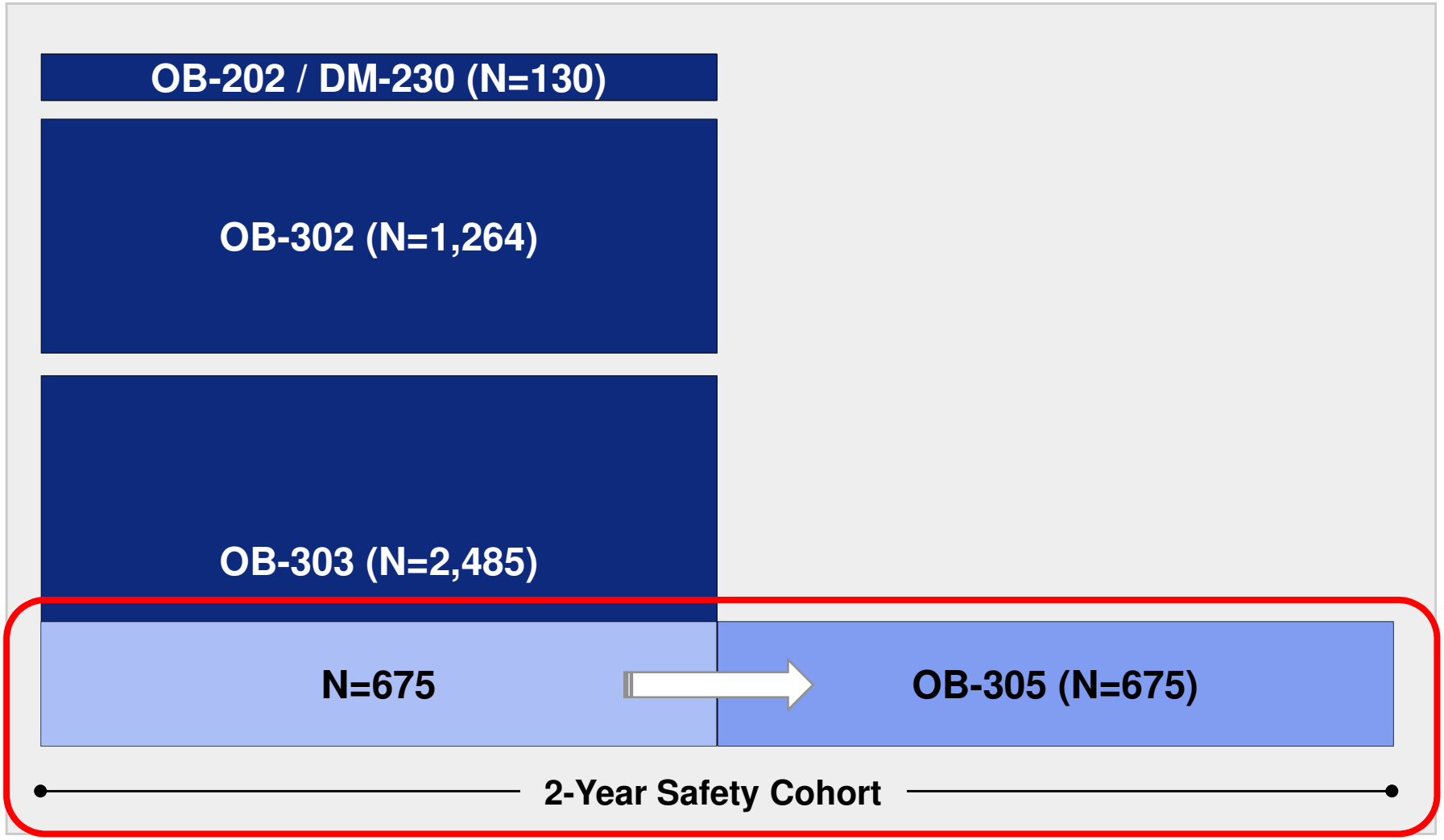
AEs with QNEXA as expected / consistent with individual drugs

[1]Kim KK, et al. *Yonsei Med J* 2006;47:614-25
[2]TOPAMAX® Package Insert 2011

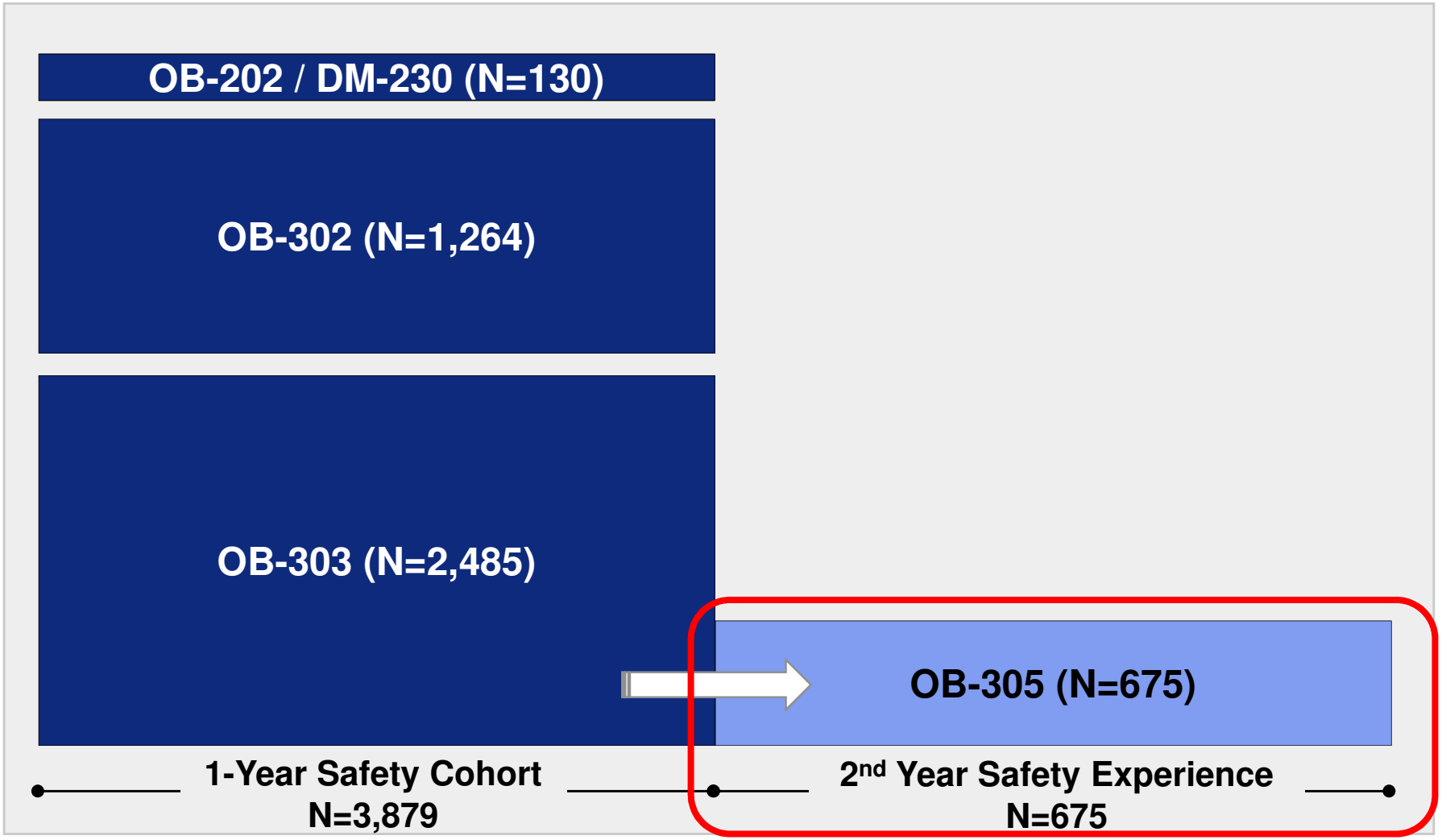
1-Year Cohort: Safety Population



1-Year Cohort vs 2-Year Cohort: Safety Population



1-Year Cohort vs 2nd Year (OB-305): Safety Population



1-Year Cohort vs 2nd Year (OB-305): 10 Most Common AEs

Incidence, %	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
Upper resp. tract infection	12.8	12.2	13.5	18.5	17.0	15.3
Constipation	6.1	15.1	16.1	3.1	7.2	4.1
Dry mouth	2.8	13.5	19.1	0.4	0.7	1.4
Paresthesia	1.9	13.7	19.9	0.0	0.7	3.4
Headache	9.3	7.0	10.6	2.6	2.6	4.1
Nasopharyngitis	8.0	10.6	9.4	11.5	8.5	8.8
Sinusitis	6.3	6.8	7.8	7.9	7.8	9.5
Insomnia	4.7	5.8	9.4	3.5	5.9	3.7
Dizziness	3.4	7.2	8.6	0.9	1.3	0.3
Back pain	5.1	5.6	6.6	3.1	5.9	5.1

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Headache	9.3	7.0	10.6	2.6	2.6	4.1
Nasopharyngitis	8.0	10.6	9.4	11.5	8.5	8.8
Sinusitis	6.3	6.8	7.8	7.9	7.8	9.5
Insomnia	4.7	5.8	9.4	3.5	5.9	3.7
Dizziness	3.4	7.2	8.6	0.9	1.3	0.3
Back pain	5.1	5.6	6.6	3.1	5.9	5.1

1-Year Cohort vs 2nd Year (OB-305): Disposition and AEs Leading to D/C

Incidence, %	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
Study completion	60.1	75.1	72.1	86.8	83.8	84.1
On drug	54.8	69.1	63.4	86.3	82.5	83.1
TEAE	76.0	85.1	87.2	80.2	72.5	79.3
TEAE leading to D/C	8.4	11.6	17.3	2.6	3.9	4.1

TE=treatment-emergent; D/C=discontinuation

1-Year Cohort vs 2nd Year (OB-305): Serious Adverse Events

Incidence, %	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
SAE	3.3	2.8	3.6	4.0	2.6	4.1

- 1 death: placebo
- No SAEs for psychiatric or cognitive disorders on QNEXA treatment
- Incidence of SAEs were similar during 1-year vs 2nd year
- No new, unexpected events appeared during 2nd year

Safety Presentation Outline

- Phentermine / Topiramate general safety
- 1-year cohort vs 2nd year (OB-305)
  - Common AEs
  - Disposition and AEs leading to discontinuation
  - SAEs
- **Safety concerns from 7/15/10 EMDAC meeting**
  - **Psychiatric TMEs**
  - **Cognition TMEs**
  - **Lowering of serum bicarbonate**
  - Increase in heart rate
  - Teratogenicity

1-Year Cohort vs 2nd Year (OB-305): TME Incidence – Psychiatric Disorders

Incidence, %	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
Sleep disorders	5.7	6.8	10.8	4.0	6.5	3.7
Anxiety	2.6	4.8	7.9	1.3	2.6	3.4
Depression	3.4	3.8	7.7	2.2	2.6	3.7
Suicide / self-injury	0.1	0.0	0.0	0.0	0.0	0.0

TME=targeted medical events

1-Year Cohort vs 2nd Year (OB-305): TME Incidence – Cognitive Disorders

Incidence, %	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
Attention	0.6	2.0	3.5	0.0	0.0	0.0
Memory Impairment	0.6	1.8	2.5	0.0	0.0	0.3
Language	0.1	0.6	1.2	0.0	0.0	0.0
Other Cognitive Disorders NOS	0.3	1.0	1.8	0.4	0.0	0.3

TME=targeted medical events; NOS=not otherwise specified

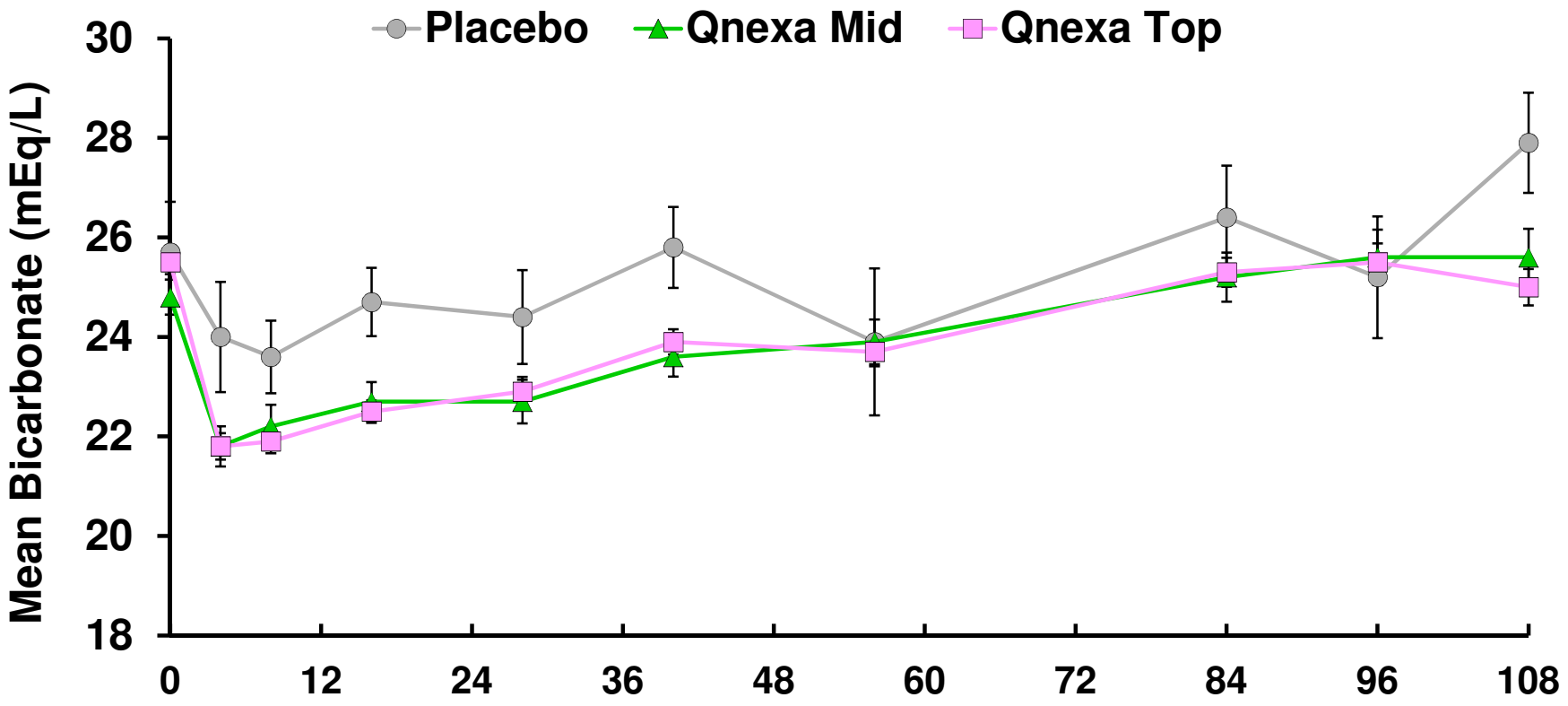
1-Year Cohort vs 2nd Year (OB-305): Persistent Serum Bicarbonate Reduction

Incidence, n (%)	1-Year Cohort			2nd Year (OB-305)		
	Placebo N=1,561	Q-Mid N=498	Q-Top N=1,580	Placebo N=227	Q-Mid N=153	Q-Top N=295
<21 mEq/L[1]	33 (2.1)	32 (6.4)	203 (12.8)	0 (0.0)	2 (1.3)	8 (2.7)
<17 mEq/L[1]	1 (0.1)	1 (0.2)	11 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Less than 21 (or 17) mEq/L at 2 consecutive measurements or at final visit

2-Year Cohort: Mean Serum Bicarbonate Values Over Time

Patients with values <21 mEq/L at any time after randomization



PBO	n=9	9
Mid	n=34	29
Top	n=90	72

Safety Summary

- AE profiles in the 2nd year (OB-305) were consistent with those in the 1-year cohort
- Psychiatric AEs, cognitive AEs, and persistently reduced serum bicarbonate occurred more with QNEXA than placebo
- No difference in SAEs, no suicidality signal in QNEXA vs placebo
- No signal of delayed or cumulative toxicity

Heart Rate and Blood Pressure: Clinical Implications

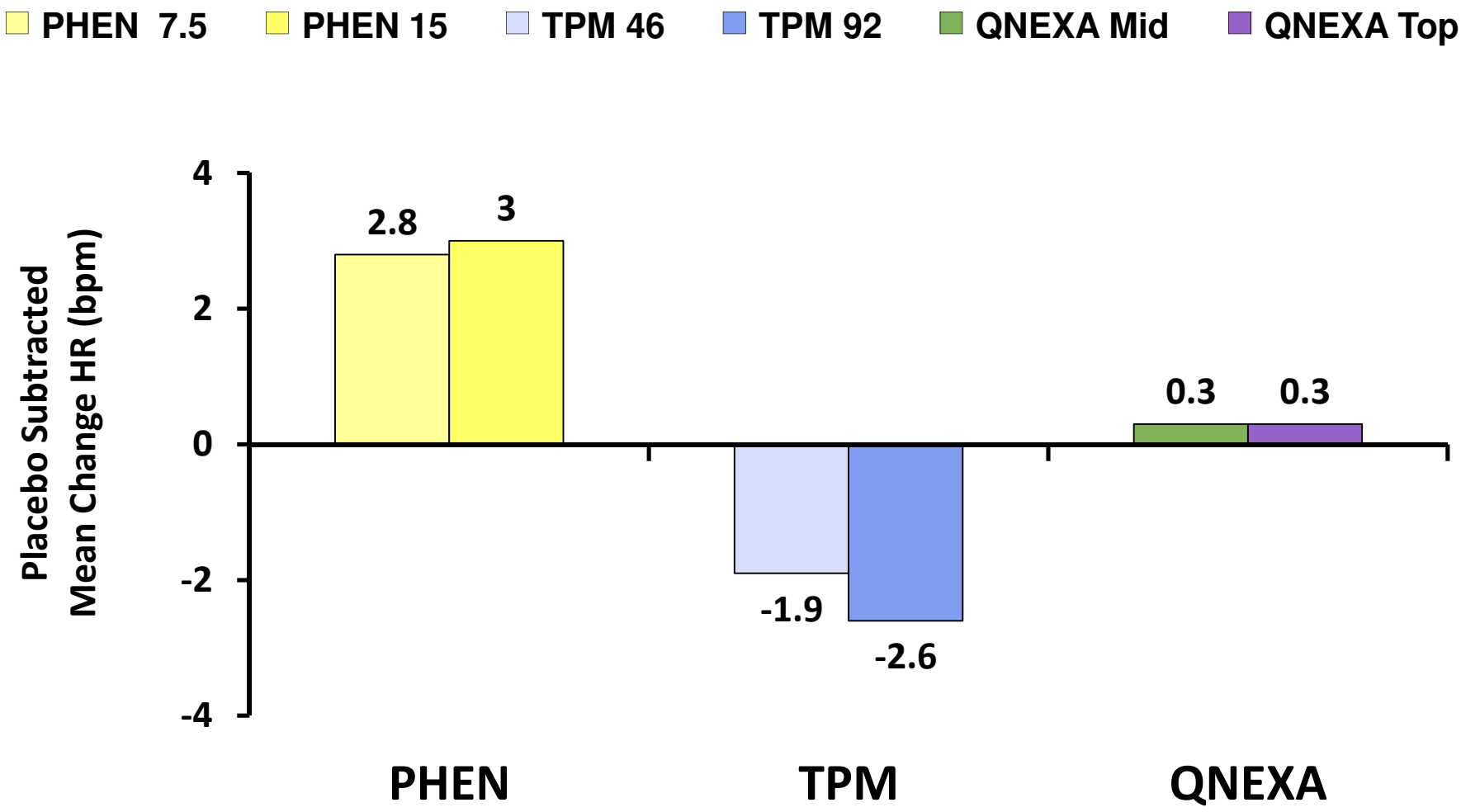
Peter R. Kowey, MD, FACC, FAHA, FHRS

Professor of Medicine and Clinical Pharmacology
Jefferson Medical College
Philadelphia, PA

Outline

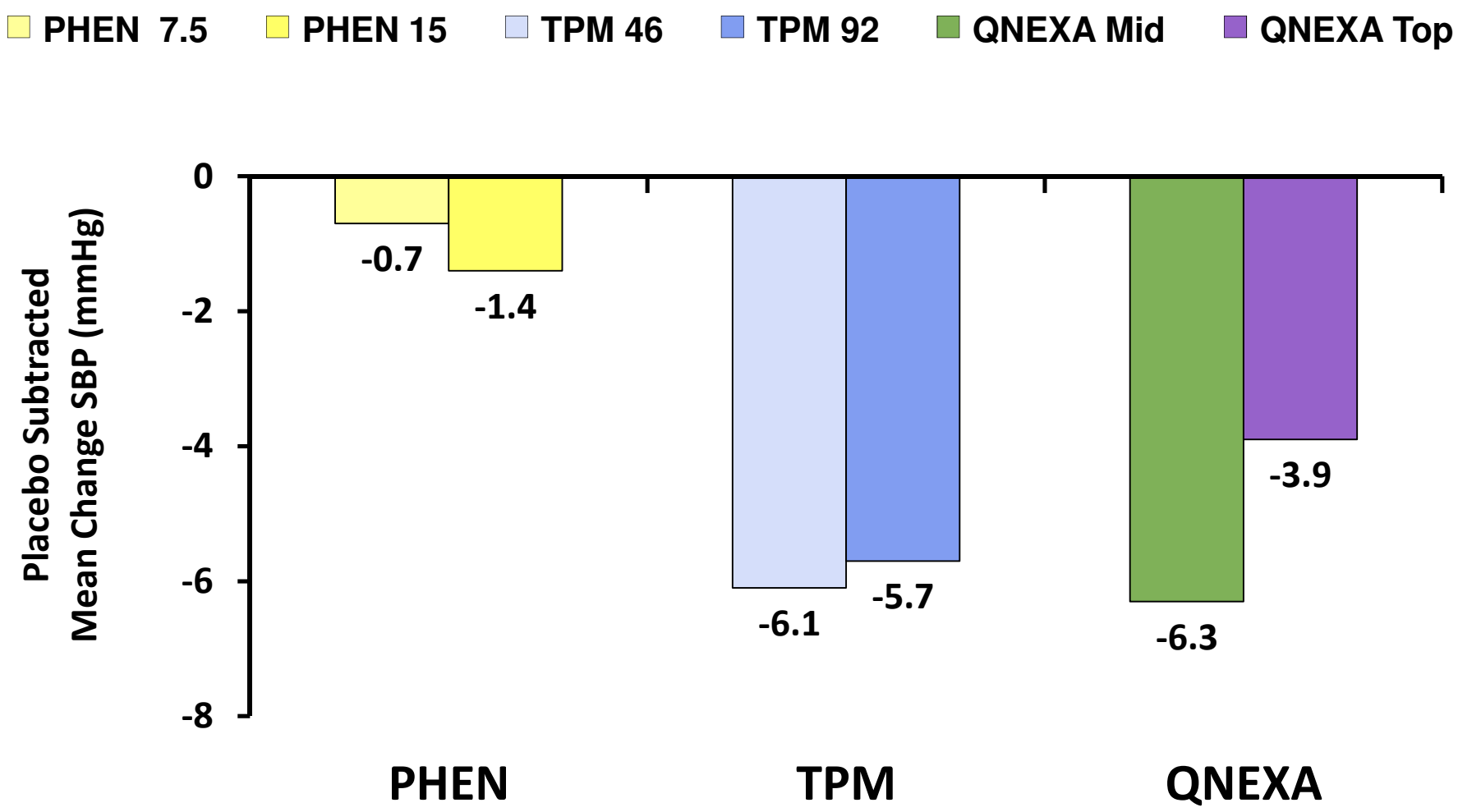
- Heart Rate
- Blood pressure
- Rate pressure product
- Outliers
- Arrhythmia adverse events
- Cardiac disorders SAEs
- MACE events

OB-301 (N=753): Mean Changes in HR at Week 28



N=Safety Population; PHEN=Phentermine; TPM=Topiramate

OB-301 (N=753): Mean Changes in SBP at Week 28



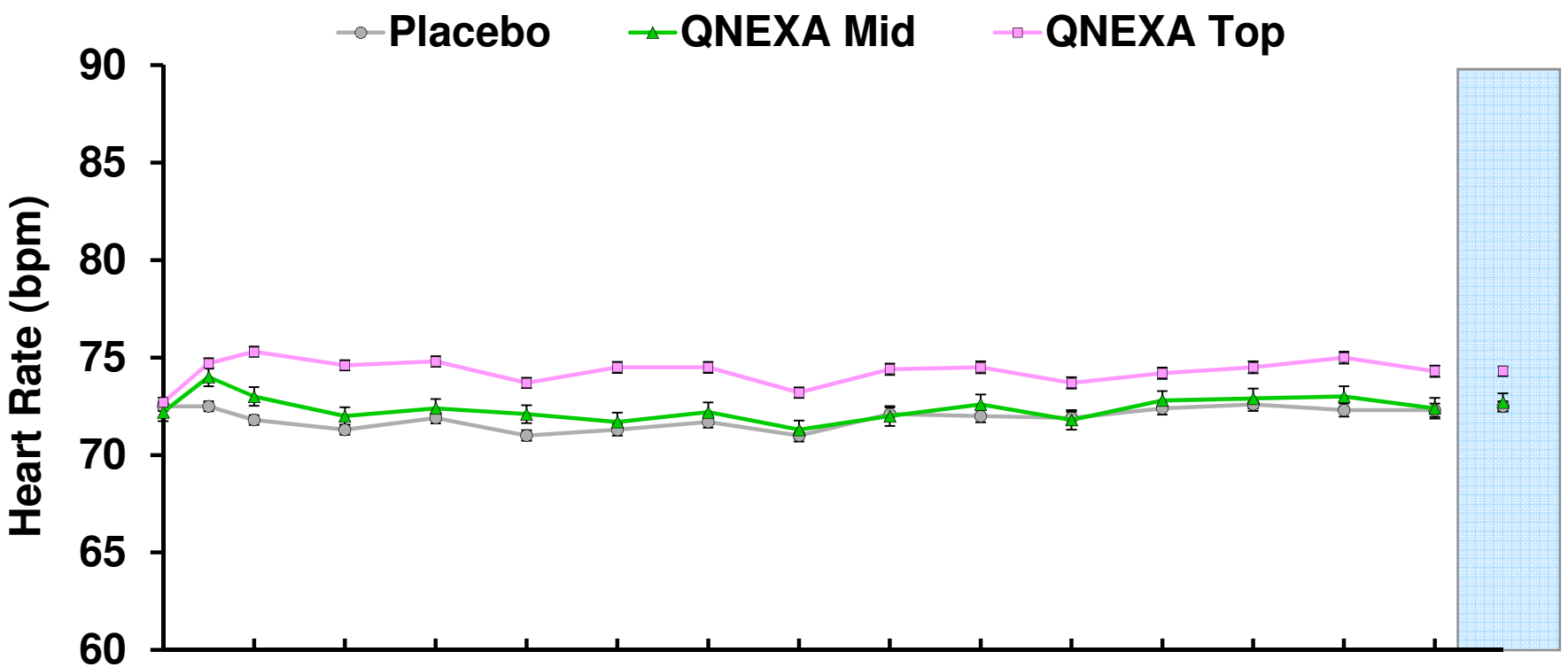
N=Safety Population; PHEN=Phentermine; TPM=Topiramate

1-Year Cohort: Mean Changes in BP and Heart Rate

Mean change to endpoint*	Placebo N=1,532	QNEXA Dose Low N=234	QNEXA Dose Mid N=488	QNEXA Dose Top N=1,553
Systolic BP, mmHg	-2.1	-3.3	-5.2‡	-5.2‡
Diastolic BP, mmHg	-1.9	-0.9	-3.3¥	-2.9¥
Heart rate, bpm	0	1.3	0.6	1.6‡

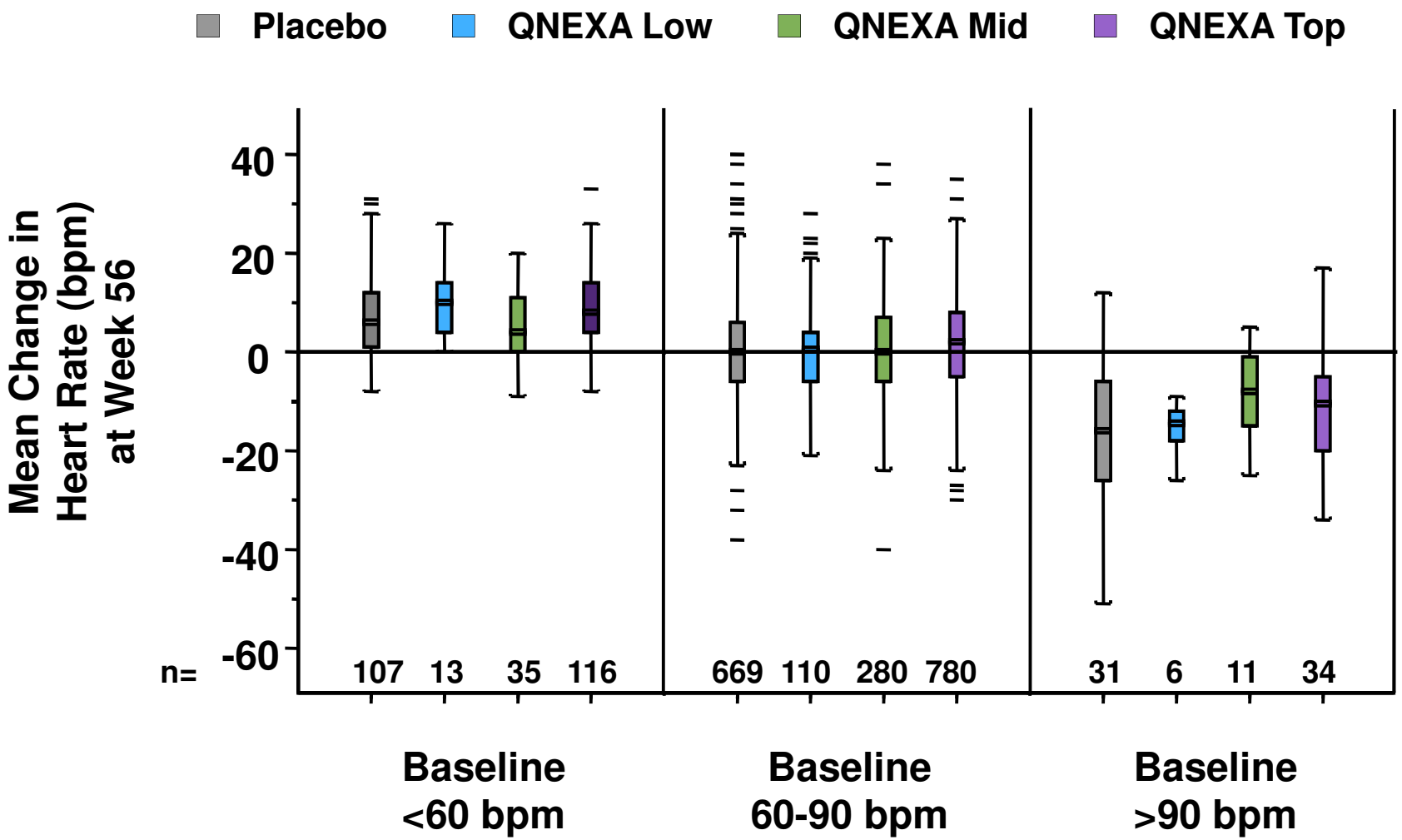
*Changes from baseline to Week 56 or early termination from study
‡p<0.0001 vs. placebo; ¥p<0.01 vs. placebo
Includes OB-302, OB-303, and OB-202/DM-230

1-Year Cohort: Heart Rate Over Time



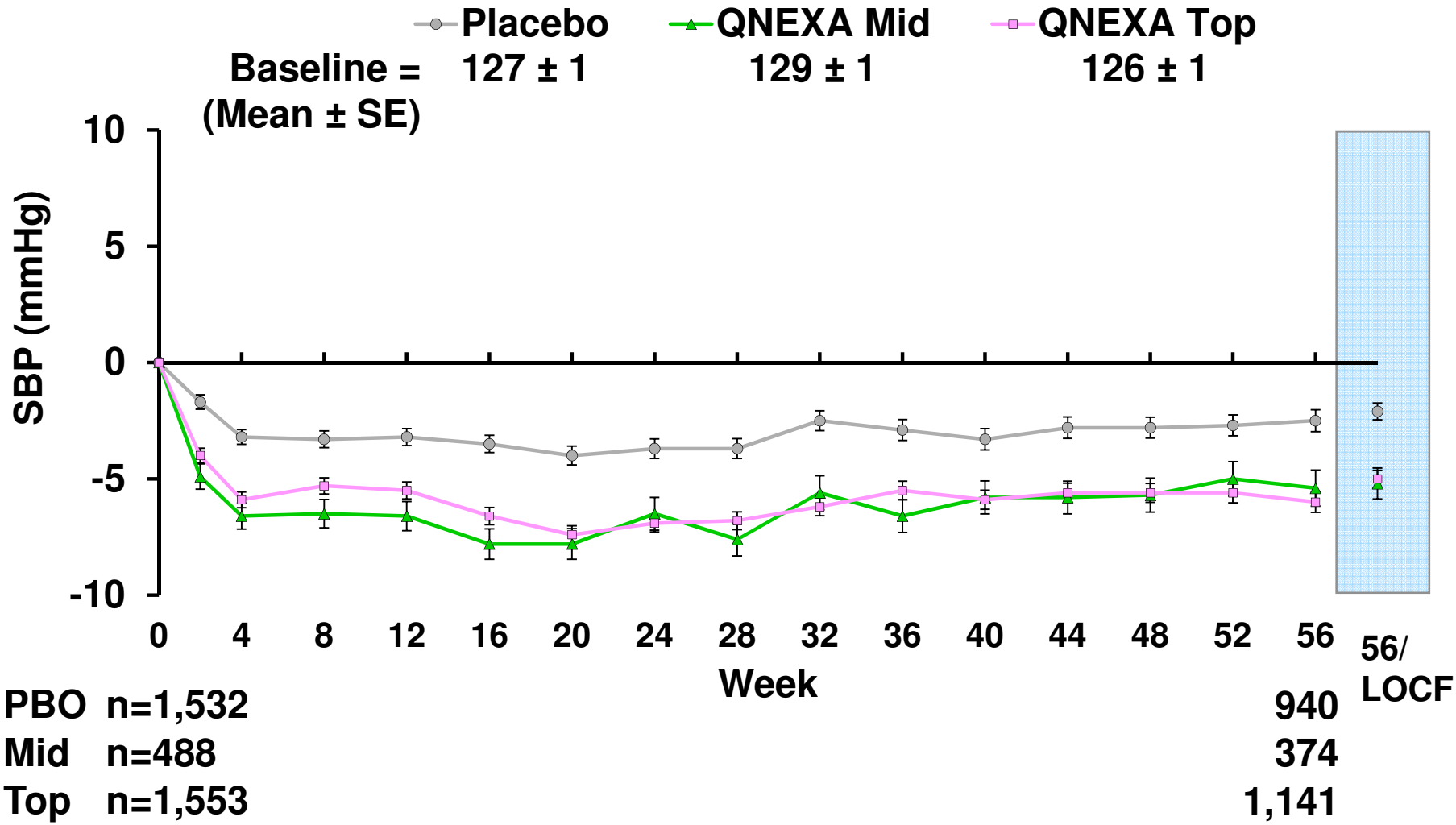
PBO	n=1,532	940
Mid	n=488	374
Top	n=1,553	1,141

1-Year Cohort: Changes in HR at Week 56 by Baseline HR

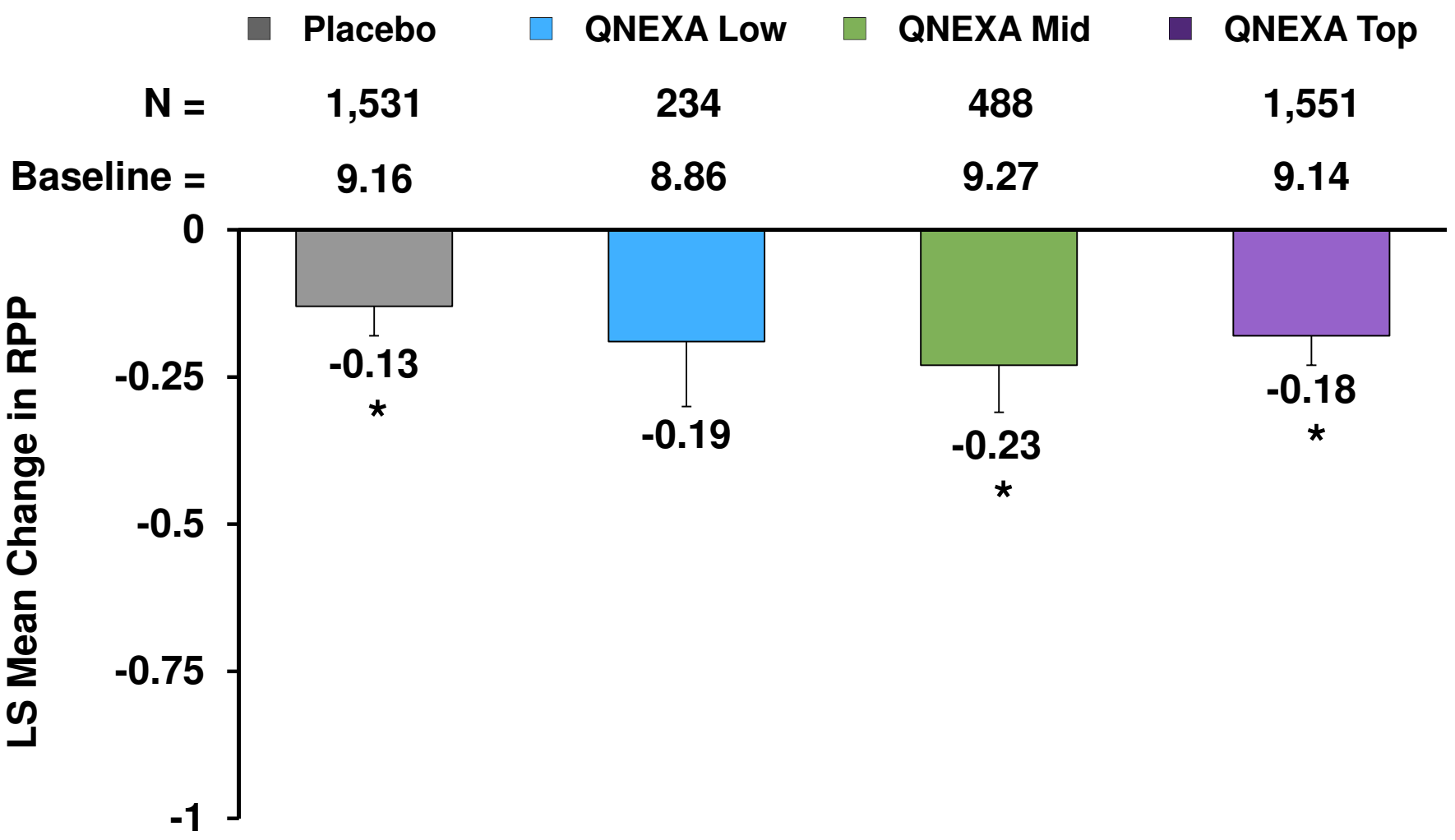


Box=25-75%; bars within box represent mean and median

1-Year Cohort: Systolic Blood Pressure Change Over Time



1-Year Cohort: Change in Rate Pressure Product



RPP is a surrogate for myocardial oxygen demand; *p-value <0.01 vs baseline

1-Year Cohort: BP and RPP
Patients With Persistent HR >100 bpm

		QNEXA Dose		
	Placebo N=1,561	Low N=240	Mid N=498	Top N=1,580
Patients with HR >20 bpm (persistent) n (%)	10 (0.6)	3 (1.3)	1 (0.2)	17 (1.1)
SBP, mmHg	128.0	129.5	131.2	122.2
DBP, mmHg	86.1	84.5	90.8	80.8
RPP ($\times 10^3$)	14.3	13.7	13.7	12.8*

*p=0.005 vs placebo; persistent=at two consecutive visits

1-Year Cohort: BP and RPP
Patients With HR >20 bpm Change from Baseline

		QNEXA Dose		
	Placebo N=1,561	Low N=240	Mid N=498	Top N=1,580
Patients with HR >20 bpm (persistent) change from baseline, n (%)	42 (2.7)	9 (3.8)	13 (2.6)	71 (4.5)
SBP, mmHg	124.5	125.3	127.9	122.2
DBP, mmHg	78.9	81.9	82.2	77.7
RPP ($\times 10^3$)	11.3	11.3	11.4	10.9

Persistent=at two consecutive visits

1-Year Cohort: Blood Pressure Outliers

		QNEXA Dose		
	Placebo N=1,561	Low N=240	Mid N=498	Top N=1,580
Systolic BP >20 mmHg	78 (5.0)	7 (2.9)	17 (3.4)	54 (3.4)
Systolic BP >30 mmHg	14 (0.9)	2 (0.8)	3 (0.6)	11 (0.7)

*Number and percent of patients with given increases at 2 or more consecutive visits

1-Year Cohort: AEs in Arrhythmia SMQ

SMQ Preferred Term, %	Placebo N=1,561	QNEXA Dose Low N=240	QNEXA Dose Mid N=498	QNEXA Dose Top N=1,580
Cardiac arrhythmia	1.8	1.3	4.2	4.7
Palpitations	0.8	0.8	2.4	1.7
Heart rate increased	0.1	0.0	0.4	0.8
Tachycardia	0.1	0.4	0.4	0.7
Syncope	0.3	0.0	0.4	0.4
Atrial fibrillation	0.1	0.0	0.2	0.2
Syncope vasovagal	0.0	0.0	0.4	0.2
RBBB	0.1	0.0	0.2	0.1
Arrhythmia	0.0	0.0	0.2	0.1
ECG abnormal	0.2	0.0	0.0	0.0
Ventricular extrasystoles	0.1	0.0	0.0	0.1

Ten most common AEs; SMQ = Standardized MedDRA Query; RBBB = Right Bundle Branch Block

1-Year Cohort: AEs in Arrhythmia SMQ

SMQ Preferred Term, %	Placebo N=1,561	QNEXA Dose Low N=240	QNEXA Dose Mid N=498	QNEXA Dose Top N=1,580
Cardiac arrhythmia	**1.8**	**1.3**	**4.2**	**4.7**
Palpitations	**0.8**	**0.8**	**2.4**	**1.7**
Heart rate increased	**0.1**	**0.0**	**0.4**	**0.8**
Tachycardia	**0.1**	**0.4**	**0.4**	**0.7**
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Ventricular extrasystoles	0.1	0.0	0.0	0.1

Ten most common AEs; SMQ = Standardized MedDRA Query; RBBB = Right Bundle Branch Block

1-Year Cohort: AEs in Arrhythmia SMQ

SMQ Preferred Term, %	Placebo N=1,561	QNEXA Dose Low N=240	QNEXA Dose Mid N=498	QNEXA Dose Top N=1,580
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Arrhythmia	0.0	0.0	0.2	0.1
ECG abnormal	0.2	0.0	0.0	0.0
Ventricular extrasystoles	0.1	0.0	0.0	0.1

Ten most common AEs; SMQ = Standardized MedDRA Query; RBBB = Right Bundle Branch Block

All Exposed Patients: Cardiac Disorders SAEs

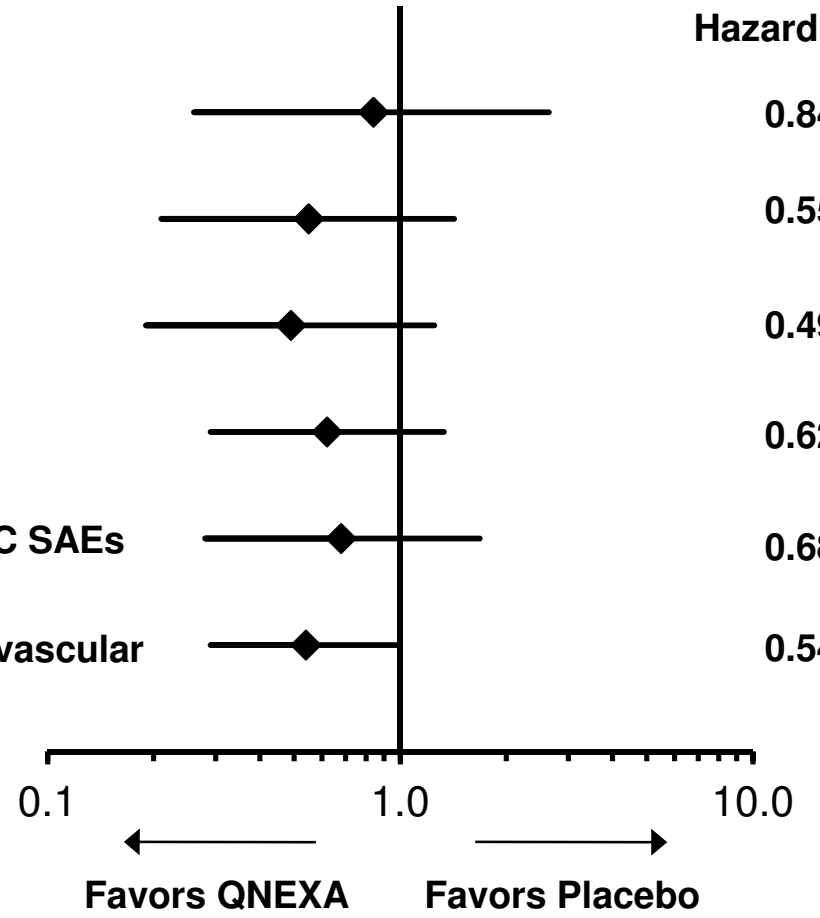
SOC Preferred Term, n (%)	Placebo N=1,742	QNEXA Dose Low N=240	QNEXA Dose Mid N=604	QNEXA Dose Top N=1,737
Cardiac Disorders	9 (0.5)	1 (0.4)	4 (0.7)	5 (0.3)
Coronary artery disease	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.4)	2 (0.3)	2 (0.1)
Atrial fibrillation	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Angina pectoris	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac failure congestive	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Includes data from studies OB-202, OB-204, DM-230, OB-301, OB-302, OB-303, & OB-305

Definitions of Cardiovascular Composite Endpoints

	Definition
CV death, MI, stroke	• CV death, MI, stroke
JUPITER MACE	• CV death, MI, stroke, coronary revascularization, hosp. for unstable angina
FDA MACE	• JUPITER MACE + heart failure
Current FDA MACE	• FDA MACE + stent thrombosis, hosp. for other CV causes, carotid artery revascularization, peripheral vascular revascularization, lower extremity amputation, and hosp. for cardiac arrhythmia
Cardiac SAEs	• SAEs in the MedDRA Cardiac Disorders SOC
CV / NV SAEs	• SAEs from cardiac SOC + DVT, hypertension, hypotension, stroke, TIA, chest pain, non-cardiac chest pain, and pulmonary embolism

All Exposed Patients: Incidence of MACE



	Hazard Ratio	95% CI	Total # Events
CV Death, MI, Stroke	0.84	[0.26; 2.64]	12
Jupiter MACE	0.55	[0.21; 1.42]	17
FDA MACE	0.49	[0.19; 1.25]	18
Current FDA MACE	0.62	[0.29; 1.33]	26
Cardiac Disorders SOC SAEs	0.68	[0.28; 1.68]	19
Cardiovascular/Neurovascular SAEs	0.54	[0.29; 0.98]	43

Cardiovascular Safety Conclusions

- 1.6 bpm increase in HR on QNEXA Top accompanied by a 5.2 mmHg ↓ in SBP
  - Clinical relevance of 1–2 bpm ↑ in HR unknown
  - Even a 2 mmHg ↓ in SBP is associated with 7% ↓ in CV morbidity / mortality and 10% ↓ in stroke[1]
- Increased heart-rate outlier patients showed concomitant decreases in BP and RPP

[1]Lewington et al, Lancet 2002

Cardiovascular Safety Conclusions (cont.)

- No increase in MACE composite hazard ratios compared to placebo
- Potential risk of small, isolated increase in HR should be considered in context of significant reductions in:
  - Blood pressure
  - TChol/HDL
  - Triglycerides
  - HbA1c
  - Insulin resistance
  - CRP
  - Fibrinogen
  - Waist circumference

Teratogenicity Potential of Topiramate

Gary Shaw, PhD
Professor
Pediatrics - Neonatal and Developmental Medicine

Stanford University School of Medicine

Deficiency Identified in FDA Complete Response Letter

- North American Antiepileptic-Drug Pregnancy Registry
  - Infants exposed to topiramate had 1.4% prevalence of oral clefts (4 / 289)
  - 10-20 fold increase in risk
- Consistent signal (with smaller N) in UK Register
- FDA requested summary of data on human teratogenic risk of topiramate

New Data Since Initial QNEXA NDA

- **Case control studies**
  - **Slone [1]**
  - **CDC[1]**
- **Cohort studies**
  - **Wolters Kluwer[2,3]**
  - **FORTRESS**

[1]Margulis AV. *Pharmacoepidemiol Drug Saf* 2011;20:S11
[2]Pack A. *29th International Epilepsy Conference*; 2011 Aug 28-Sep1; Rome, Italy
[3]Green M. *136th Annual meeting of the Am Neurological Assn*; 2011 Sep 25-27; San Diego, CA

Two Large US Case-Control Studies

- Slone Epidemiology Center Birth Defects Study 1997 - 2009 (Slone)
- National Birth Defects Prevention Study 1996 - 2007 (CDC)

Slone Epidemiology Center Birth Defects Study

	No AED	Topiramate	Adjusted OR	95% CI
Control	6933	2	Reference	
MCM	10,503	5	1.2	0.2, 13.0
Oral clefts	778	3	10.1	1.1, 129.2

MCM = major congenital malformations

CDC
National Birth Defects Prevention Study

	No AED	Topiramate	Adjusted OR	95% CI
Control	8434	4	Reference	
MCM	23,102	10	0.9	0.3, 4.1
Oral clefts	2256	4	3.6	0.7, 20.0

MCM = major congenital malformations

Slone and CDC Combined

	Topiramate	Adjusted OR	95% CI
Control	6	Reference	
MCM	15	1.0	0.4, 3.2
Oral clefts	7	5.4	1.5, 20.1

MCM = major congenital malformations

Slone and CDC Summary

- No apparent association between topiramate and major congenital malformations
- Topiramate during first trimester may be associated with increase risk of oral clefts

Cohort Studies Sponsored by VIVUS

- Wolters Kluwer (~40 million persons)
- FORTRESS (~70 million persons)
  - OptumInsight
  - HealthCore
  - Multi-State Medicaid (Thompson-Reuters)
  - Kaiser Permanente

Cohort Studies: Wolters Kluwer

- Mother-infant dyads with medical and drug claims
- Cohort of women exposed to topiramate in first trimester
- Comparator cohorts:
  - First trimester exposure to other AEDs
  - Epilepsy (no topiramate)
  - Random dataset sample
  - Diabetes (positive control)

AED = Antiepileptic drugs

Wolters Kluwer Study: Major Congenital Malformations

First trimester exposure	N with MCMs	# of Live Births	Prevalence (%)	RR Topiramate vs Comparator (95% CI)
Topiramate	**37**	**870**	**4.3**	**NA**
Comparison Group:				
Epilepsy	**113**	**2607**	**4.3**	**1.0 (0.7, 1.4)**
Other AED	**116**	**3615**	**3.2**	**1.3 (0.9, 1.9)**
Random sample	**3758**	**99,761**	**3.8**	**1.1 (0.8, 1.6)**
Diabetes	**859**	**13,062**	**6.6**	**0.7 (0.5, 0.9)**

AED = Antiepileptic drugs; MCM = major congenital malformations

Wolters Kluwer Study: Oral Clefts

First trimester exposure	N with Oral Clefts	# of Live Births	Prevalence (%)	RR Topiramate vs Comparator (95% CI)
Topiramate	**2**	**870**	**0.23**	**NA**
Comparison Group:				
Epilepsy	**8**	**2607**	**0.31**	**0.8 (0.2, 3.5)**
Other AED	**6**	**3615**	**0.17**	**1.4 (0.3, 6.9)**
Random sample	**159**	**99,761**	**0.16**	**1.4 (0.4, 5.8)**
Diabetes	**34**	**13,062**	**0.26**	**0.9 (0.2, 3.7)**

AED = Antiepileptic drugs

Cohort Studies: FORTRESS

- Four major claims datasets
- Cohorts
  - Topiramate: total, and monotherapy
  - Former exposure to topiramate or other AED
  - Similar medical profile
- Oral clefts identified through claims
  - Previously validated with greater than 90% PPV[1]

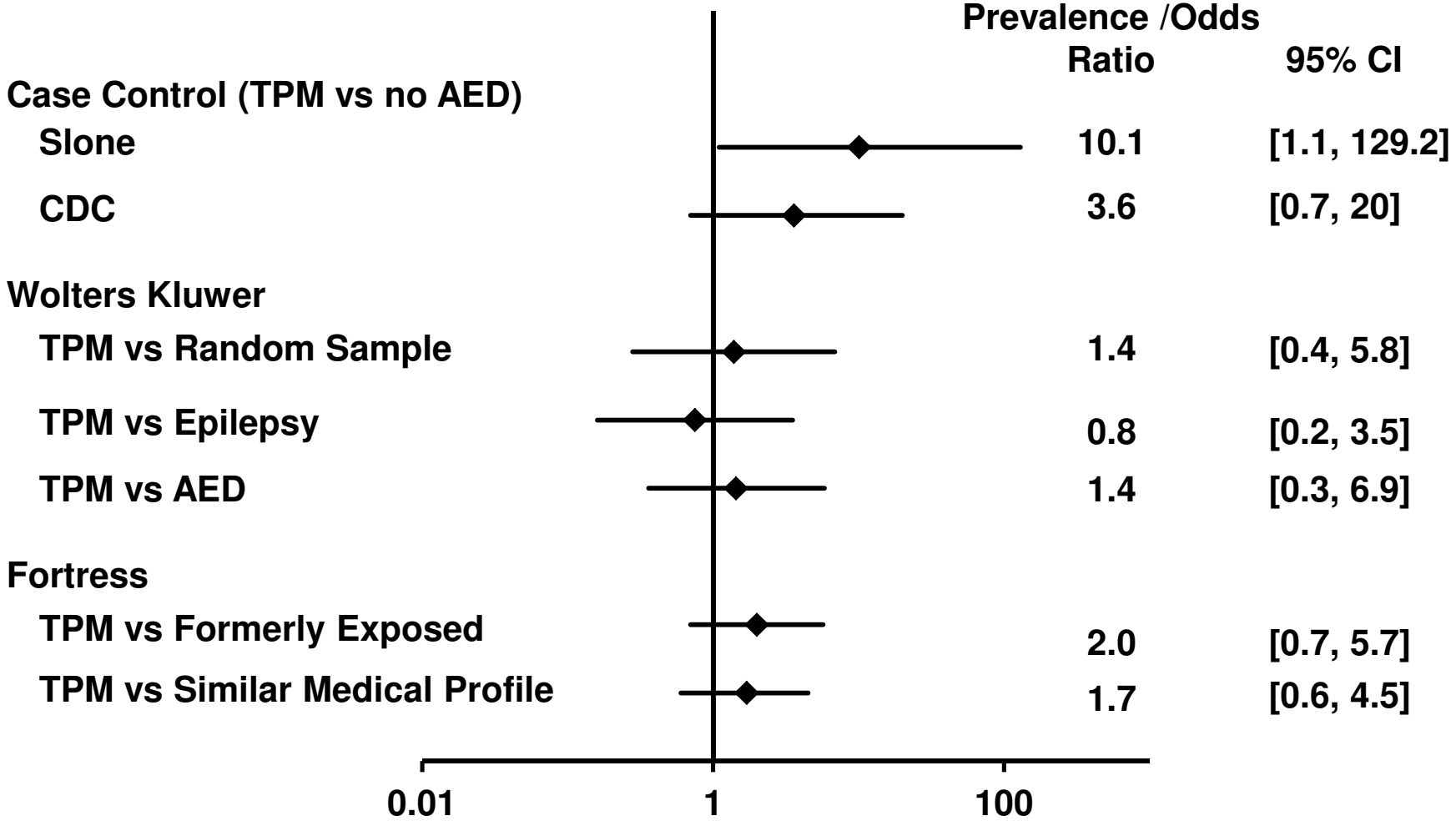
[1]Cooper et al, *Pharmacoepidemiology and Drug Saf*, 2008.

FORTRESS: Oral Clefts

First trimester exposure	N with Oral Clefts	# of Live Births	Prevalence (%)	PR [1]Topiramate vs Comparator (95% CI)
Topiramate Monotherapy	**5**	**1740**	**0.29**	**NA**
Comparison Group:				
Formerly Exposed	**21**	**13,512**	**0.15**	**2.0 (0.7, 5.7)**
Similar Medical Profile	**383**	**247,614**	**0.16**	**1.7 (0.6, 4.5)**

[1] Prevalence Ratio (Topiramate vs. Comparator) adjusted for center-specific propensity score decile

Topiramate Monotherapy: Oral Clefts



TPM = topiramate; AED = antiepileptic drugs

Summary and Conclusions

- Topiramate may be associated with a 2- to 5-fold increase in risk of oral clefts
- Risk difference is low; 1.3 additional clefts per 1000 exposed pregnancies/births
- Topiramate does not appear to be associated with increased risk of major congenital malformations overall
- Obesity and diabetes are consistent risk factors for major congenital malformations

Clinical Perspective on Teratogenic Potential of Topiramate

Anthony Scialli, MD

Clinical Professor of Obstetrics and Gynecology, George Washington University School of Medicine

Director, Reproductive Toxicology Center, Washington, D.C.

Risks of Obesity in Pregnant Mother

- Gestational diabetes
- Preeclampsia
- Cesarean delivery
- Surgical complications
- Postpartum hemorrhage
- Thromboembolic disease
- Infections

ACOG, Obstetric Practice, Obesity in Pregnancy, 315, 2005
AOGS, Nohr, Mortality in Infants of Obese Mothers, 2011

Risks of Maternal Obesity to Child

- Infant mortality
- Stillbirth
- Spontaneous abortion
- Macrosomia
- Shoulder dystocia
- Prematurity
- Congenital malformation

ACOG, Obstetric Practice, Obesity in Pregnancy, 315, 2005
AOGS, Nohr, Mortality in Infants of Obese Mothers, 2011

Cardiology Perspective

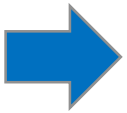
A. Michael Lincoff, MD

Vice Chairman, Dept of Cardiovascular Medicine,
The Cleveland Clinic

Obesity Confers Cardiovascular Risk

Proposed Mechanisms

- Diabetes
- Hypertension
- Increased LDL
- Increased TG/HDL ratio
- Endothelial dysfunction and platelet activation
- Inflammation
- Obstructive sleep apnea



Outcomes

- CV death
- MI
- Stroke
- Heart failure
- Atrial fibrillation

Risk of obesity is additive to conventional risk factors (e.g., Framingham Risk)

CV Risk Factors

Changing Phenotype

Progress made in:

- Tobacco use
- Untreated hypertension
- LDL-cholesterol

Less or No Progress in:

- Diabetes
- Resistant hypertension
- HDL-cholesterol
- Triglycerides
- Sedentary lifestyle

Surrogate Endpoints or “Biomarkers”

Biomarker	Accepted as Regulatory Endpoint	Effect of QNEXA
Blood pressure		
Heart rate		
Total chol/HDL		
Triglycerides		
HbA1c		
Progression to T2DM		
Insulin resistance		
CRP		
Fibrinogen		
Waist circumference		

Surrogate Endpoints or "Biomarkers"

Biomarker	Accepted as Regulatory Endpoint	Effect of QNEXA
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Heart rate	No	
Total chol/HDL	No	
Triglycerides	No	
HbA1c	Yes	
Progression to T2DM	Yes	
Insulin resistance	No	
CRP	No	
Fibrinogen	No	
Waist circumference	No	

Surrogate Endpoints or "Biomarkers"

Biomarker	Accepted as Regulatory Endpoint	Effect of QNEXA
Blood pressure	Yes	Beneficial
Heart rate	No	Not beneficial
Total chol/HDL	No	Beneficial
Triglycerides	No	Beneficial
HbA1c	Yes	Beneficial
Progression to T2DM	Yes	Beneficial
Insulin resistance	No	Beneficial
CRP	No	Beneficial
Fibrinogen	No	Beneficial
Waist circumference	No	Beneficial

No apparent signal of CV harm

A Cardiologist's Perspective

- **Obesity is important to treat**
  - Portends increased CV risk
  - Even if mediated by traditional risk factors, makes those risk factors more difficult to manage
  - Important and unmet clinical need
- **QNEXA produces striking beneficial effect on obesity**
- **QNEXA was not associated with adverse cardiovascular "signal"**
  - Does not share adverse hypertensive effects of other anti-obesity agents
  - Of many unvalidated surrogates, one (pulse rate) moves in negative direction, while all others move in positive direction
  - BP, a sufficient surrogate for CV disease, favorably influenced
  - No suggestion of more frequent CV events

Obesity:
Why Doing Nothing is Not an Option

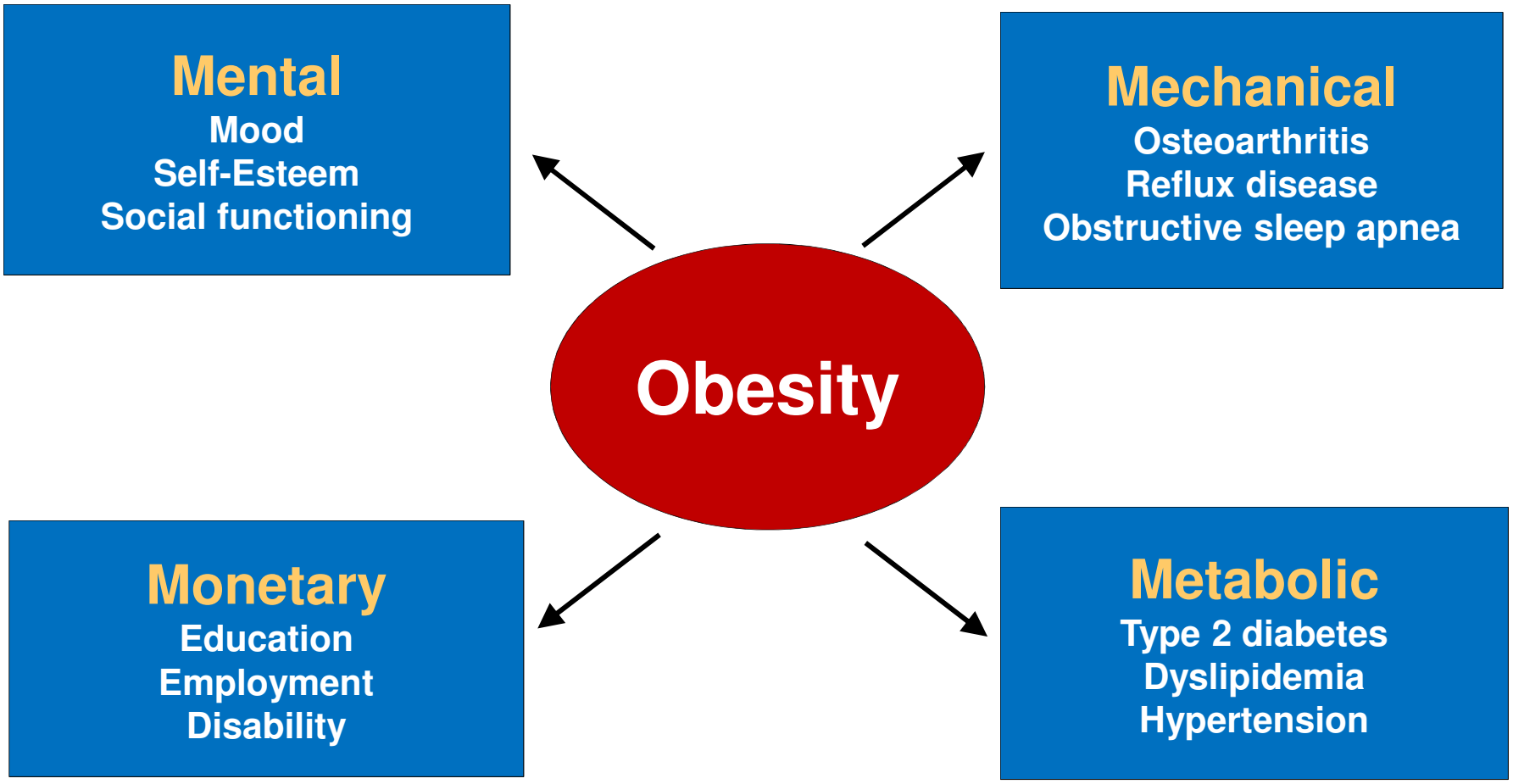
Arya M. Sharma, MD/PhD, DSc (h.c.), FRCPC

Professor of Medicine
Chair in Obesity Research & Management
University of Alberta
Edmonton, Alberta

Outline

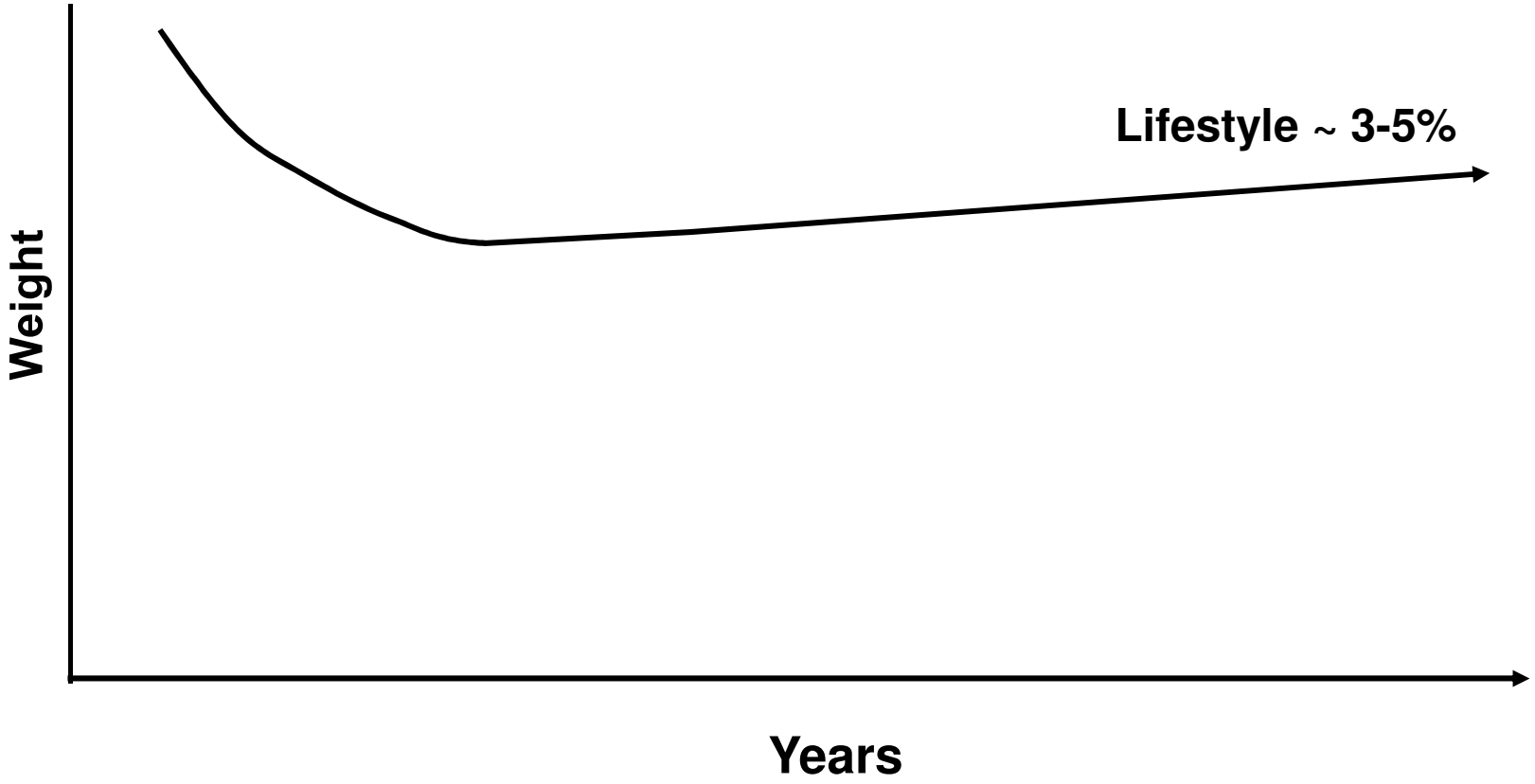
- Health impact of obesity
- Unmet medical need of addressing the ‘therapeutic gap’
- Risk / benefit considerations

Obesity Effects and Complications

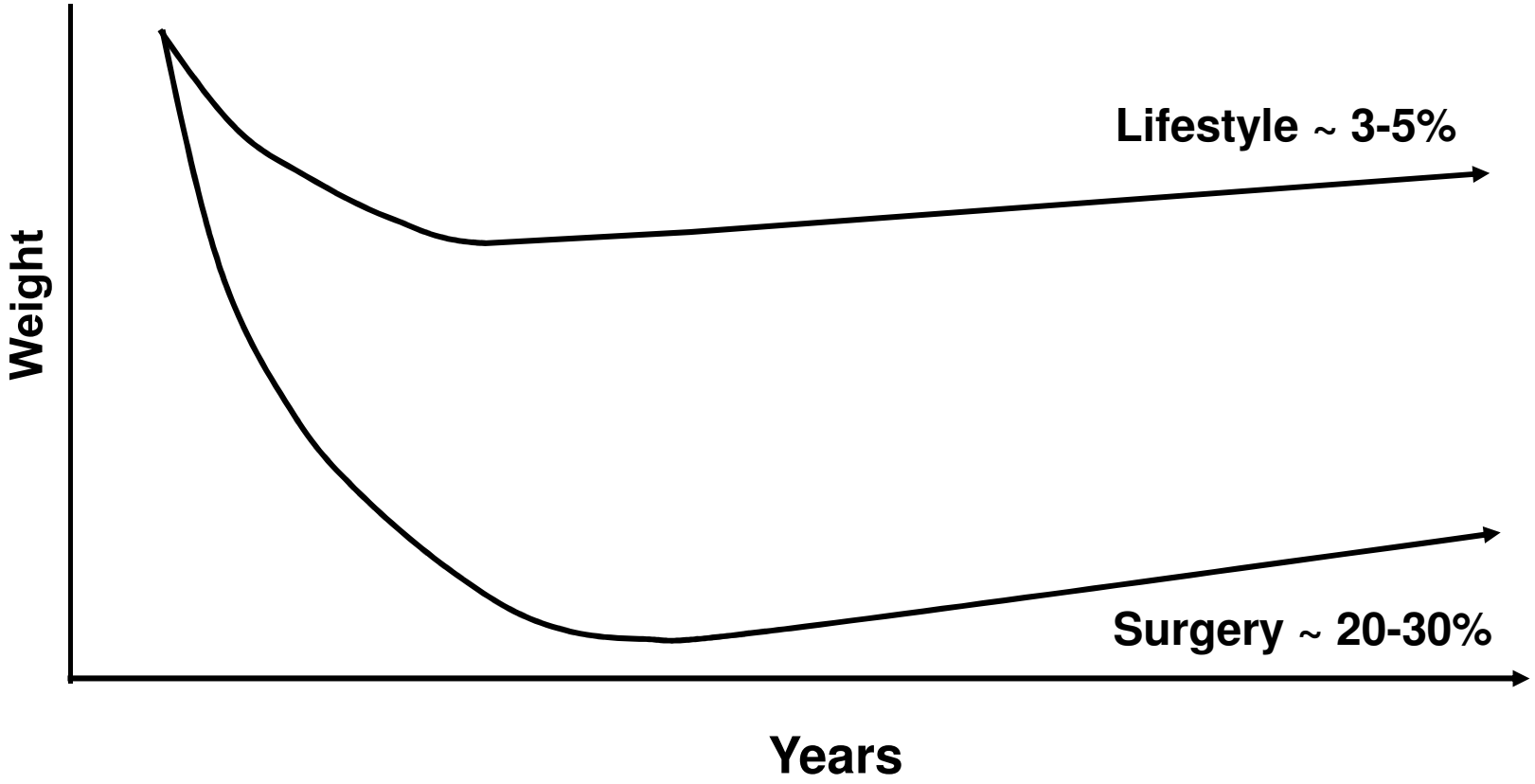


Adapted from Sharma AM, *Obes Rev* 2010

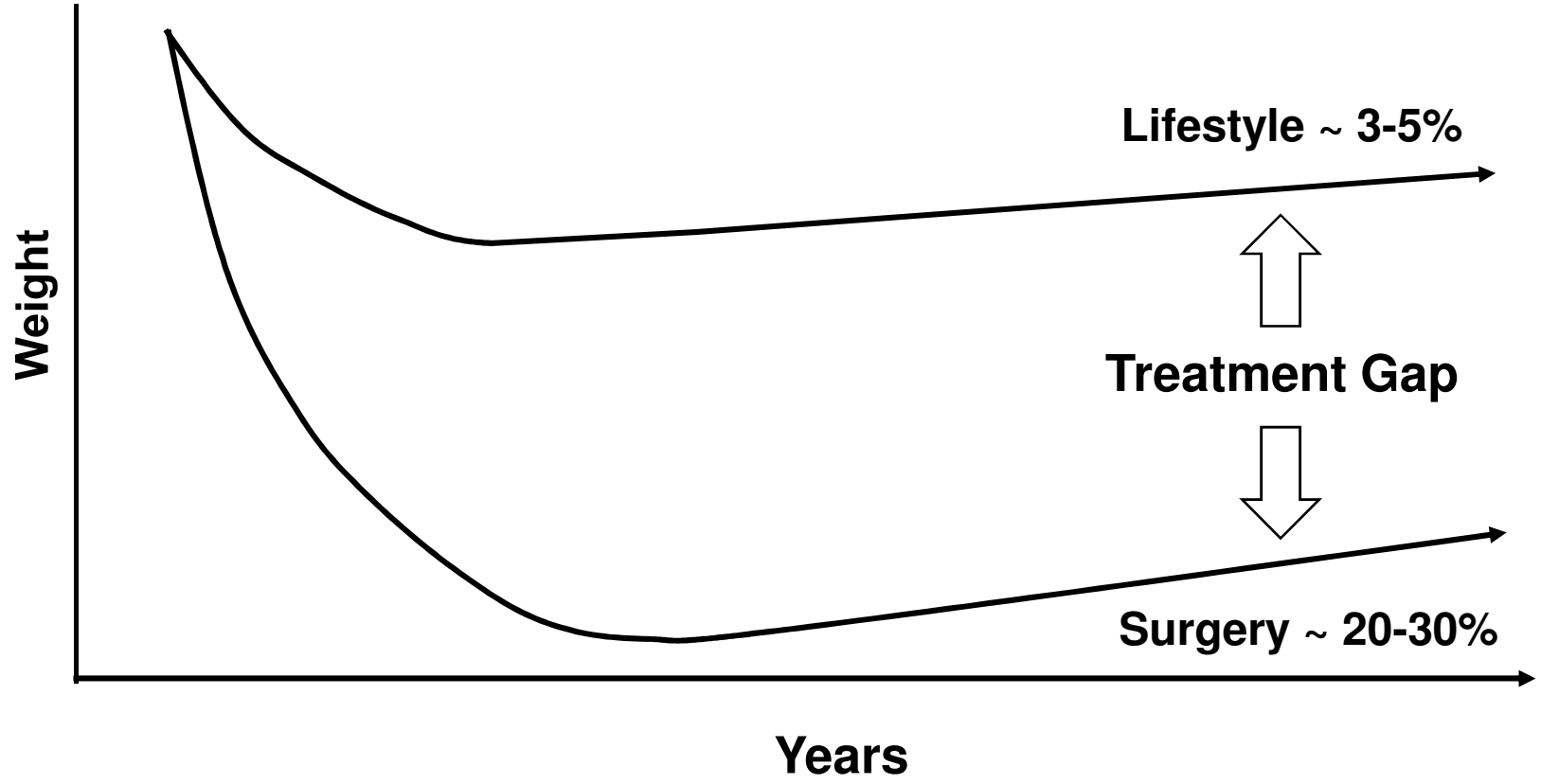
Typical Treatment Success



Typical Treatment Success



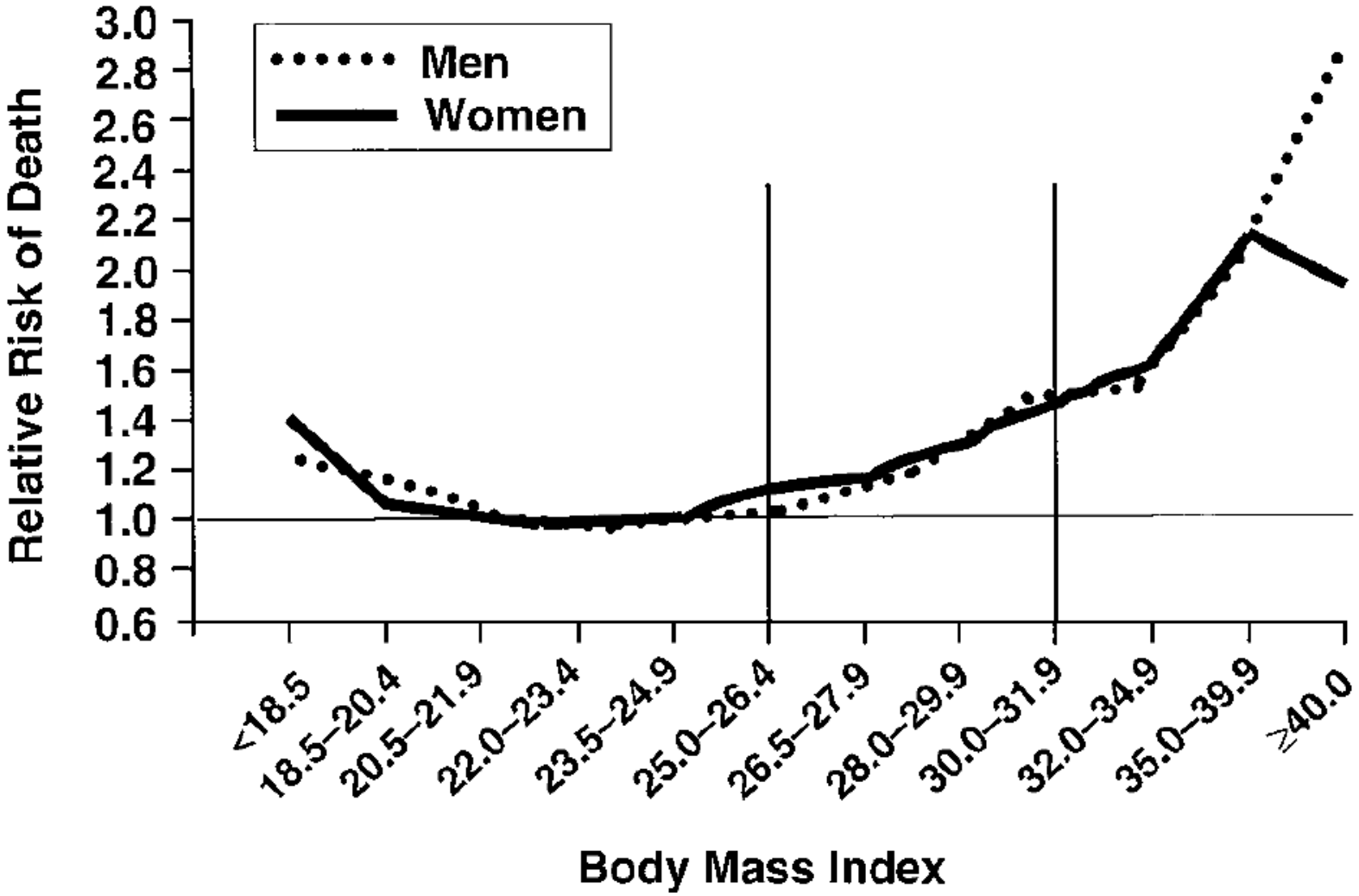
Typical Treatment Success



When To Treat?

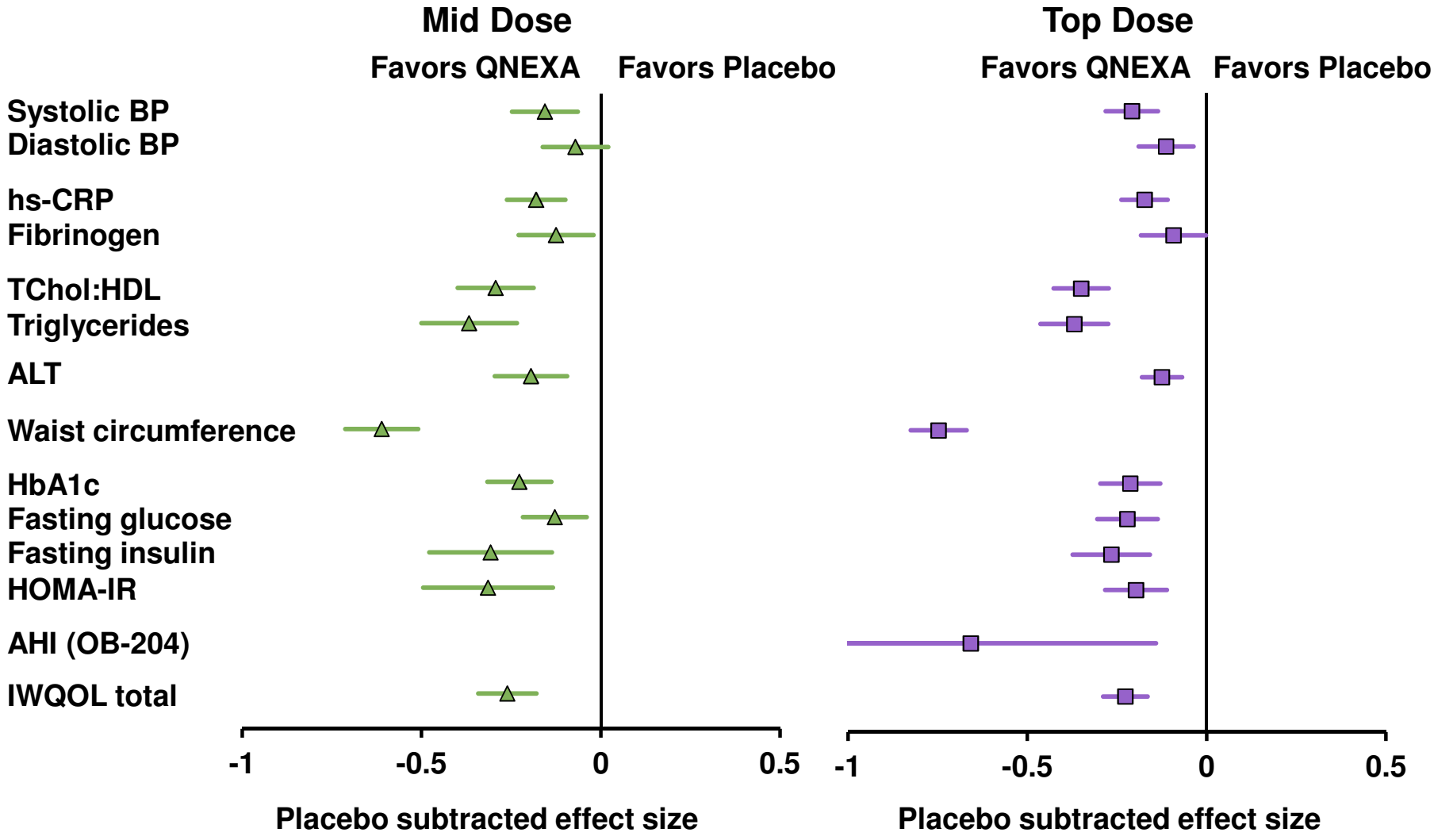
When the risk of not treating exceeds the risk of treating, then treat.

BMI and Risk of Cardiovascular Mortality



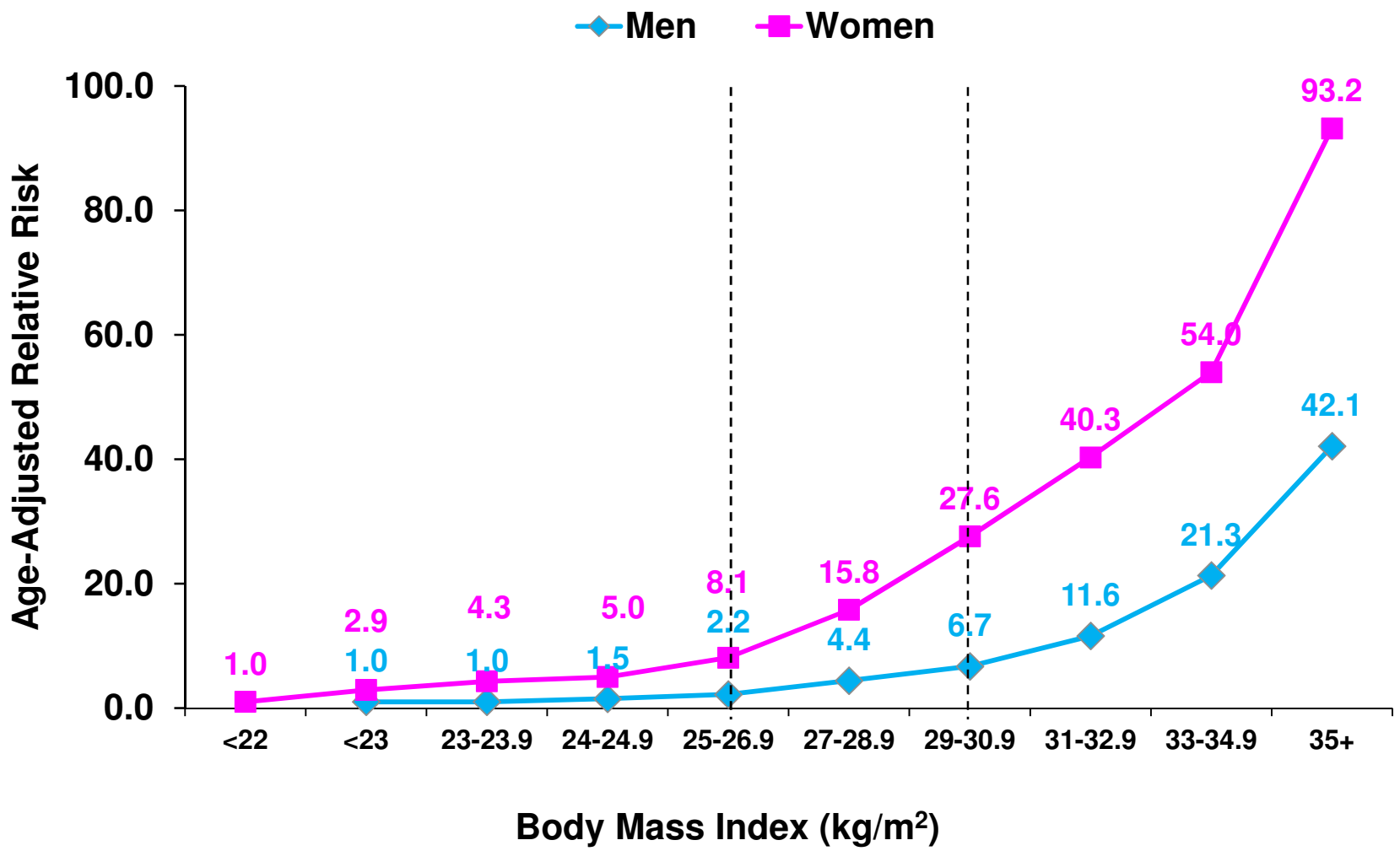
Calle et al, NEJM 2000

Effects on Weight-Related Co-Morbidities



ITT; Effect size calculated as mean change divided by SD

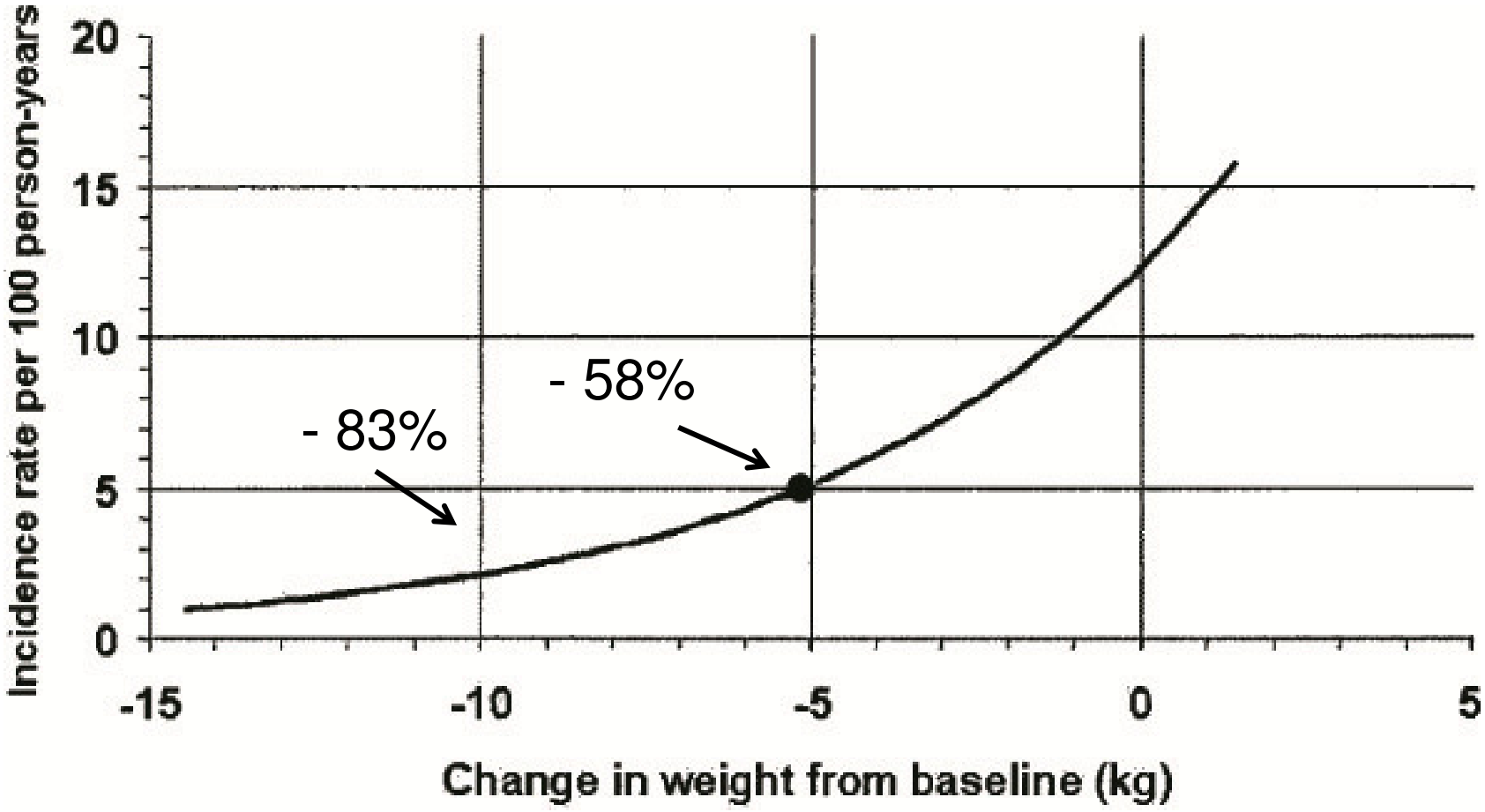
Relationship Between BMI and Risk of Type 2 Diabetes



Chan J, et al. *Diabetes Care.* 1994;17:961-969. Colditz G, et al. *Ann Intern Med.* 1995;122:481-486.

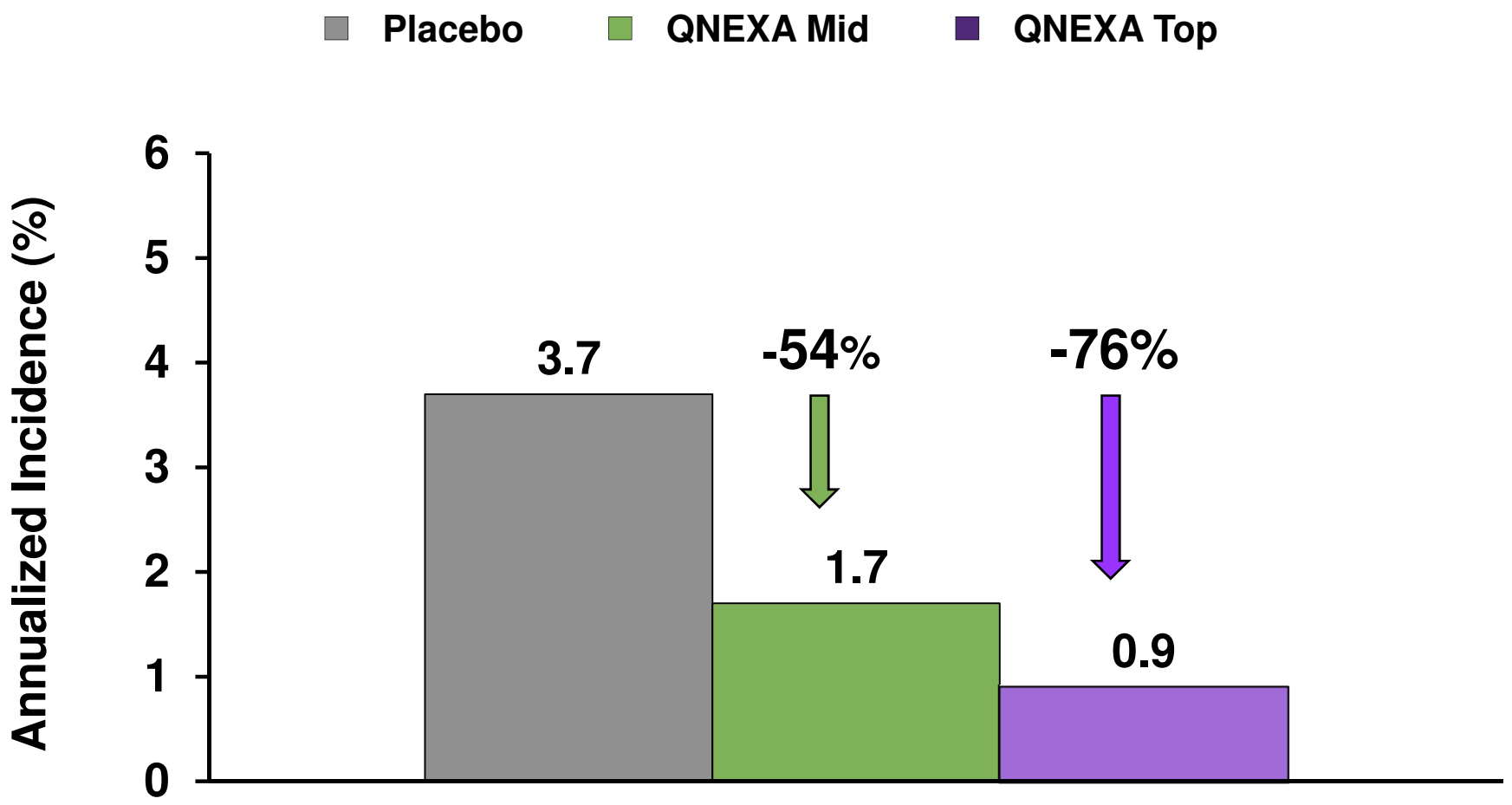
Diabetes Prevention & Weight Change: Diabetes Prevention Program (DPP)

Diabetes Incidence (per 100 Person-Years) by Change in Weight After Baseline

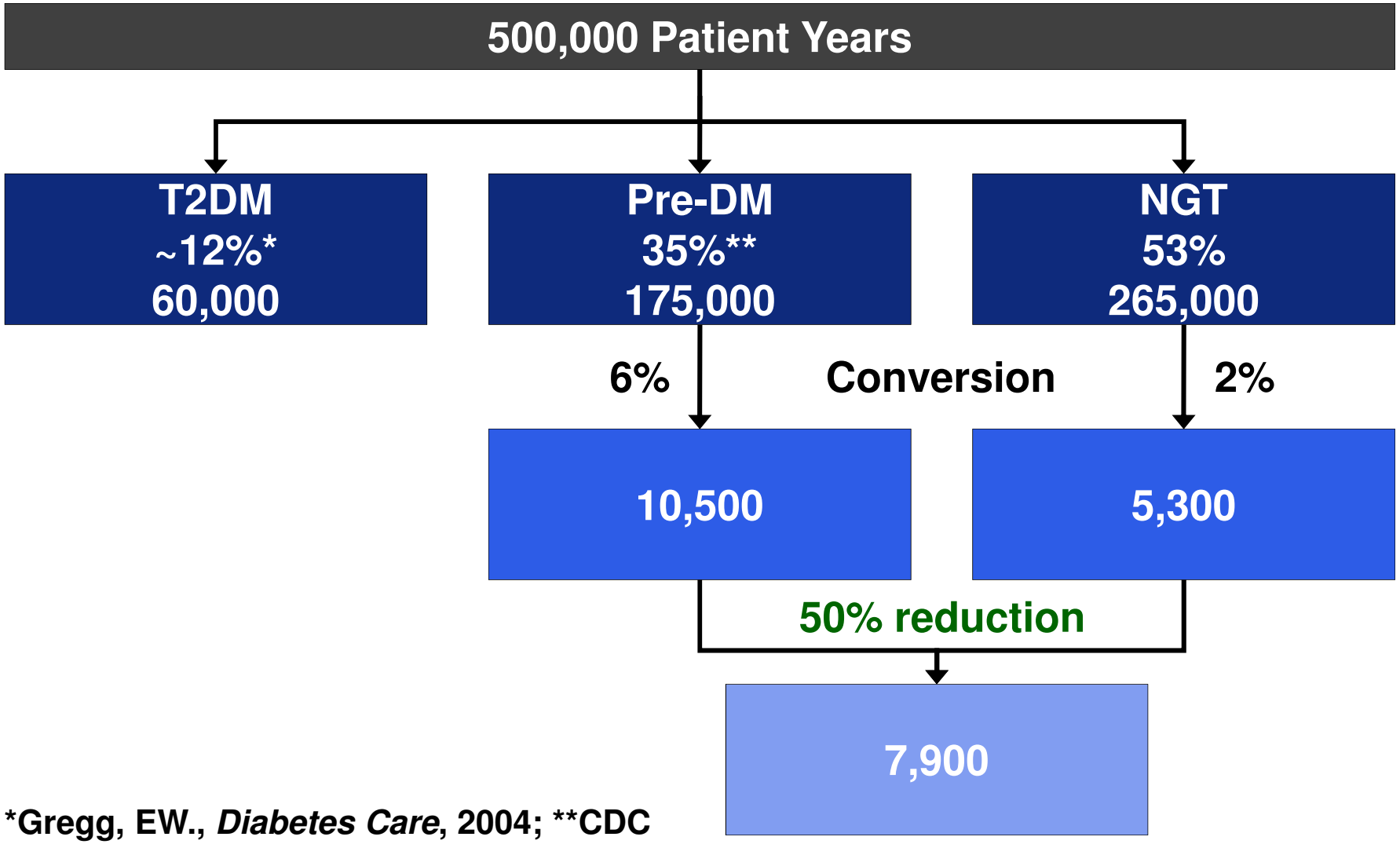


Adapted from Hamman, et al, *Diabetes Care* 2006

Slowing Progression to Diabetes: QNEXA OB-305 (2-Year)



Reduction in New Cases of T2DM in Patients Treated with QNEXA



*Gregg, EW., *Diabetes Care*, 2004; **CDC

The Opportunity to Make a Difference

- QNEXA addresses a substantial unmet need for antiobesity pharmacotherapy
- The risk/benefit ratio of QNEXA appears clearly on the side of benefit
- Appropriate measures can be adopted to ensure that these benefits reduce the burden of obesity on our patients

Risk Mitigation

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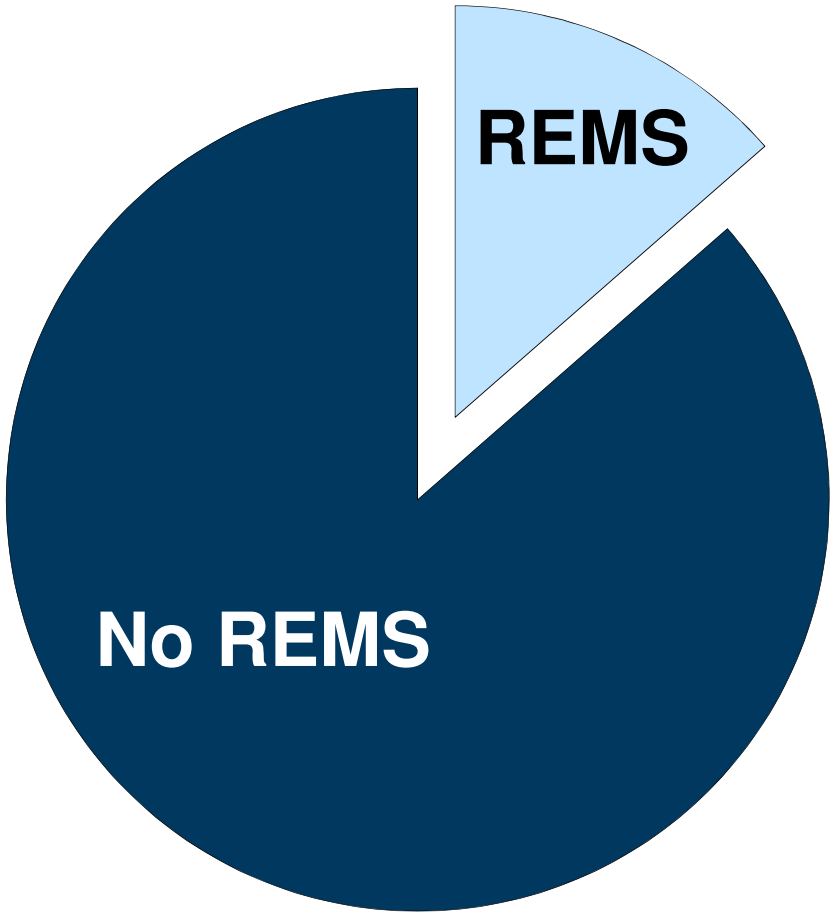
Risk Mitigation in Context

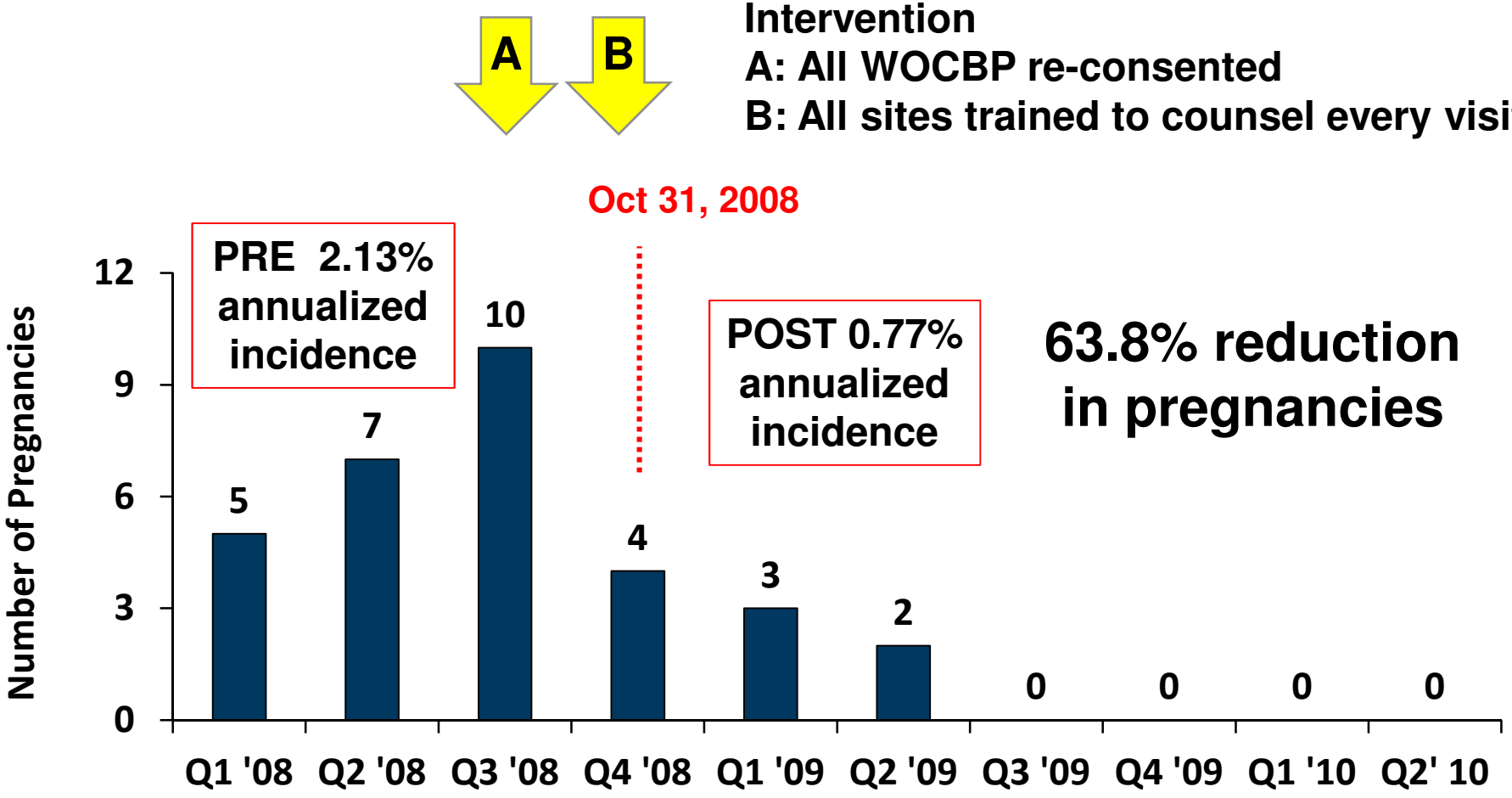
- FDA-approved risk mitigation programs for Category X drugs
- QNEXA Phase 3 program learnings

REMS Programs and Category X

Of 59 Category X drugs, only 8 have a REMS program



Phase 3 – Reduction in Pregnancy Rate



QNEXA Risk Mitigation Objectives

- Prevent pregnancies
- Minimize fetal exposure
- Focus on appropriate patient selection
- Maintain patient access without undue barriers

Key Safe Use Messages

- Importance of appropriate patient selection
- Potential risk of teratogenicity (oral clefts)
- Importance of adequate birth control
- Pregnancy testing before, during treatment
- Discontinue QNEXA if pregnant
- Awareness of Pregnancy Registry

Comprehensive Risk Mitigation Program

Labeling

- Contraindication
- Warnings
- Special Populations
- DEA Scheduling

REMS

- Medication Guide
- Communication Plan
- ETASU - Controlled Distribution
- ETASU - Provider Training

Additional Measures

- Patient-Provider Agreement
- Contraceptive Counseling Brochure
- Pregnancy Registry

Comprehensive Risk Mitigation Program

Labeling

REMS

Additional Measures

Proposed QNEXA Labeling

Section	
Contra-indication	▪ QNEXA is contraindicated in women who are pregnant ▪ If a patient becomes pregnant while taking QNEXA, treatment should be discontinued immediately
Warnings	▪ Discontinue treatment immediately if pregnant ▪ Description of risk of oral clefts
Specific Populations	▪ Pregnancy Category X ▪ Pregnancy Registry ▪ Use adequate birth control, recommend pregnancy testing before/during treatment
DEA Scheduling	▪ Schedule IV (due to phentermine)

Comprehensive Risk Mitigation Program

Labeling

REMS

Additional Measures

QNEXA REMS Goals

- **Inform prescribers, pharmacists, patients about. . .**
  - **Potential risk of oral clefts associated with fetal exposure to QNEXA**
  - **Importance of pregnancy prevention, need to minimize fetal exposure**
  - **Safe use conditions for QNEXA**

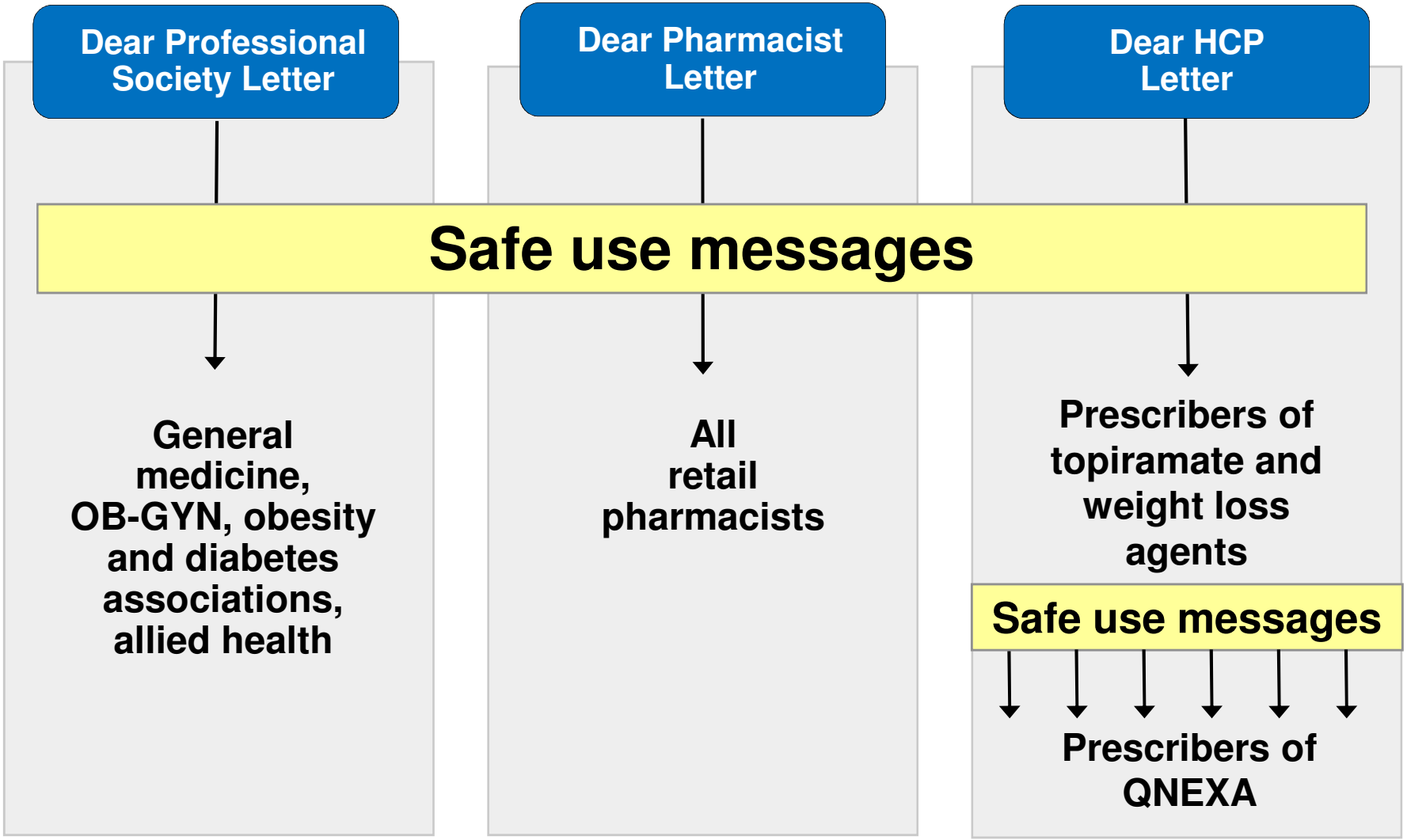
Overview of QNEXA REMS

Element	Purpose
Medication Guide	▪ Inform patients regarding teratogenic risk ▪ FDA-approved, patient-focused labeling to communicate safe use information to patients
Enhanced Communication Plan	▪ Inform prescribers regarding teratogenic risk ▪ Create awareness of the REMS
Elements To Assure Safe Use (ETASU)	
- Pharmacy Certification	▪ Control pharmacy access through certification
- Provider Training	▪ Provide training for healthcare providers

Medication Guide

- Provided with each prescription and refill, every 30 days
- Reinforces key safety messages on
  - Contraception
  - Pregnancy testing
  - Discontinuance if pregnant and existence of Pregnancy Registry
- Also includes information on other risks

Enhanced Communication Plan



ETASU:
Certified Controlled Pharmacy Network

- Limited number (<10) of largest, certified mail order pharmacies
- This is the only channel to dispense QNEXA
  - No internet access, no stock bottles, no resale, no sampling
- Allows development of databases to target safe use messaging to providers and patients
- Facilitates accurate and timely REMS assessments
- Provides systematic distribution of Med Guide, reinforcing use of contraception and pregnancy testing

ETASU:
Training for Healthcare Providers

- **Focus on current and potential prescribers**
  - Continuously available online
  - Also available through professional society meetings
- **Risk information and clinical guidance on safe and appropriate use**
- **Targeted use of prescriber data to close gaps**

QNEXA REMS Assessments

Component	Assessment
Medication Guide	▪ Patient surveys ▪ Verify pharmacy distribution
Communication Plan	▪ HCP surveys
ETASUs	▪ Pharmacy certification compliance ▪ Rates of prescriber training
Timetable for Submission of Assessments	
Assessments	▪ 6, 12, 24, 36, 48, 60, 72, and 84 months post-REMS approval

Comprehensive Risk Mitigation Program

Labeling

REMS

Additional Measures

Additional Measures

- Patient-Provider Agreement
- Contraceptive Counseling Brochure
- Pregnancy Registry

Comprehensive Risk Mitigation Program

Topiramate Risk Mitigation in Context

	Topiramate (as currently labeled)	QNEXA
Pregnancy Category	**Cat D (Cat C until 2011)**	**Cat X**
REMS Requirement	**No (released June 2011)**	**Yes**
Medication Guide	**As part of label**	**Yes**
Communication Plan	**No**	**Yes**
ETASU – Controlled Distribution	**No**	**Yes**
ETASU – Provider Training	**No**	**Yes**
Program Assessments	**No**	**Yes**

QNEXA Risk Mitigation Program Summary

- Pharmacy network controls access to QNEXA, facilitates safety communication and assessments
- Broad educational initiative making patients/providers aware of teratogenicity risk
- Pregnancy Category X labeling
- Assessments designed for early, frequent review
- Additional measures support implementation within existing health care system to minimize burden yet reinforce safe use